Access and Use of Information Resources in Assessing Health Risks From Chemical Exposure

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Preface

Health risk assessment is based on access to comprehensive information about potentially hazardous agents in question. Relevant information is scattered throughout the literature, and often is not readily accessible. To be useful in assessment efforts, emerging scientific findings, risk assessment parameters, and associated data must be compiled and evaluated systematically. The U.S. Environmental Protection Agency (EPA) and Oak Ridge National Laboratory (ORNL) are among the federal agencies heavily involved in this effort.

The ORNL involvement in this effort is effected primarily through its Biomedical and Environmental Information Analysis Section (BEIA). This group has evolved in response to the 1961 recommendation of the President's Science Advisory Committee that information resources should be developed that would focus on the data and information being generated from research on the interactions of potentially hazardous agents within biological and environmental systems. BEIA fulfills this mission through the collection of experimental information from many sources and the development of value-added information products and systems such as documents, databases, expert systems, and literature collections.

One of EPA's primary responsibilities is to control and regulate chemical release to the environment. Because information is the foundation of meaningful risk assessments on which to base environmental decisions, ready access to health, environmental, and regulatory information is central to EPA's mission. State and local agencies are becoming increasingly involved in risk assessment, particularly site-specific assessments, making EPA's information transfer and risk communication burden even heavier. Clearly, in today's environment, accurate, consistent, and concise information is essential to ensure that all parties involved in risk assessment are appropriately informed.

This symposium was a direct response by EPA and ORNL to the expressed needs of individuals involved in assessing risks from chemical exposure. In an effort to examine the state of the risk assessment process, the availability of toxicological information, and the future development and transfer of this information, the symposium provided an excellent cadre of speakers and participants from state and federal agencies, academia, and research laboratories to address these topics. This stimulating and productive gathering discussed concerns associated with (1) environmental contamination by chemicals; (2) laws regulating chemicals; (3) information needs and resources; (4) applications; (5) challenges and priorities; and (6) future issues. Displays and hands-on demonstrations of EPA and ORNL information resources were highlights of the symposium.

These proceedings consist of 38 papers contributed mostly by platform speakers and panel discussants. The papers are arranged to emulate the symposium program, with a few editorial insertions, and organized into 9 sections as presented in the Table of Contents. In addition to the complete text of papers presented during platform sessions, abstracts for the poster and demonstration presentations are included in the Appendix.

A symposium of this magnitude requires the efforts and talents of many people, and we want to thank all of those who helped. We are especially grateful to Wilma Barnard and Ida Miller for the many hours they devoted to making the symposium successful and to Marilyn Langston and Dorla Arnwine for their work preparing this volume for publication. We would also like to thank David Reisman for his contribution in the planning of this symposium, as well as Norma Cardwell of the ORNL Conference Office for her help with arrangements.

Finally, the organizing committee would like to thank the more than 230 participants, speakers, and poster and demonstration presenters for their contributions, which helped make the symposium a worthwhile effort for all.

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Symposium Introduction

Some time ago, Dr. Bill Farland, Dr. Chris DeRosa, Dave Reisman, John Wassom, and I discussed putting forth the effort to organize this symposium. We decided to focus on information resources because people evaluating risk from environmental contaminants must have access to the best information resources available to carry out their regulatory or research missions. To accomplish our purpose, we provided a list of important topics to be addressed by subject experts during the symposium. We have brought together over 230 registered participants from 30 states: representatives from federal agencies, academia, industry, and research laboratories throughout the continental United States. We also have with us a special group of attendees, teachers from several local school systems and some consultants from the Tennessee Department of Education.

We are indeed very excited about the program we have planned for the symposium. All of us are aware of the crucial need for reliable and comprehensive information for use in assessing health risks from chemical exposure. Those who are specifically charged with the task of making such assessments know that much pertinent information is scattered throughout the literature and is difficult to locate and obtain. New scientific findings of interest to the risk assessment process must be systematically compiled, evaluated, and made available to those who need it. This symposium will address this need.

During this 3-day symposium, through hands-on demonstrations, discussions, poster sessions, and formal platform presentations, many speakers will address the symposium's basic theme—information resources for health risk assessment. We have developed sessions on chemical health effects and information needs; toxicology information resources; and application of toxicology information for establishing priorities for chemical testing, hazard ranking, and assessment. Guidelines used by the U.S. Environmental Protection Agency (EPA) to assess toxicological hazards will also be discussed. A poster and demonstration session will acquaint participants with some of the information resources pertinent to health risk assessment that are available from EPA and ORNL. In addition, three different panel sessions will address ways that federal and state agencies use information resources in health risk assessment applications. Presentation topics include information files and data resources development, communication, and technology transfer. On the last day, a panel will review the issues, challenges, and concepts discussed during the first two days. Finally, our concluding speaker will address the question, "Where do we go from here?"

We appreciate the support of our symposium cohosts at the EPA Office of Health and Environmental Assessment in Washington, D.C.; the EPA Environmental Criteria and Assessment Office in Cincinnati, Ohio; and the Biomedical and Environmental Information Analysis Section of Oak Ridge National Laboratory.

Po-Yung Lu, Oak Ridge National Laboratory

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The Problem of Living in a World Contaminated With Chemicals

Robert L. Metcalf, University of Illinois

The proliferation of xenobiotic chemicals in the global environment poses living problems for each of us aboard "spaceship earth." Seven case studies are presented that illustrate the magnitude of the problem that can result from waiting to identify toxic hazards until there have been decades of "human guinea pig" exposure.

Introduction

The past century witnessed an exponential growth in the number of synthetic chemicals considered essential to science and technology. The *Merck Index*, 1st edition (1889), listed only 828 chemicals; the 11th edition (1990) lists more than 10,000. More than 44,000 different chemicals are identified in the U.S. Environmental Protection Agency (EPA) Toxic Substances Control Act Inventory (1979). During the past 50 years, the volume of synthetic organic chemical production in the United States has increased 20-fold, from 10 billion pounds annually in 1943 to about 200 billion pounds in 1989 (U.S. Tariff Commission data).

The proliferation of these xenobiotic chemicals in the global environment poses living problems for each of us aboard "spaceship earth," whether these chemicals are micropollutants of air, water, and food; are bioconcentrated through food chains; permeate the work place; or are destructive to the ozone layer. The problems of living with these chemicals will become more acute as the world population increases from 5.3 billion in 1990 to an estimated 17 billion by the year 2050. This huge population increase will be accompanied by a concomitant demand for even greater chemical production for use in the manufacture of fuels, plastics, plasticizers, fibers, elastomers, solvents, detergents, paints, pesticides, food additives, and pharmaceuticals. It has been estimated that every year more than 500 new and potentially toxic chemicals are produced on a scale large enough that traces of them enter the environment through air, water, and directly and indirectly into food. We are well along into a period picturesquely described by *Time Magazine* as the "Age of Effluence" (May 10, 1968).

A World Health Organization (WHO) report, "Microchemical Pollution in the Environment" (1963), emphasized that such chemicals present at parts per billion (ppb) to parts per trillion (ppt) levels can be harmless, toxic, or carcinogenic. During the past 50 years we have learned, at great cost, that many substances "generally regarded as safe" can be extraordinarily hazardous to humans, other life forms, and to the total quality of

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the environment. The ubiquitous use of asbestos is a case in point! Seven case studies are presented here that illustrate the magnitude of the problem that can result from waiting to identify toxic hazards until there have been decades of "human guinea pig" exposure.

Tetraethyl Lead

Lead tetraethyl [$(C_2H_5)_4Pb$] was developed in 1922 by Midgley and Boyd as an "antiknock" substance to prevent predetonation in internal combustion engines. The use of tetraethyl lead in the United States increased proportionately with the growth of the automobile industry, and in 1970, approximately 360 million pounds of tetraethyl lead was consumed. At that time the average lead content of gasoline was 2.6 g/gal. Lead is released in automobile exhausts primarily as an aerosol of lead chlorobromide (PbClBr) with a median particle diameter of about 0.25μ. As a result, atmospheric concentrations of lead range from 0.3 mg/m^3 in rural areas to 1.4 mg/m^3 in average urban locations. Concentrations in areas congested with heavy traffic are much higher, e.g., Los Angeles freeway areas containing as much as 38 mg/m^3 (Ewing and Pearson 1974). The influence of leaded fuel automobile exhausts on lead in the environment is enormous, as shown by investigations of lead content in the Greenland ice cap, which rose about fourfold in ice deposited over the period of 1930 to 1950 (Murozumi et al. 1969).

Although lead has been known as a toxic metal since antiquity, "the lead from automobile exhausts was widely perceived as inconsequential" despite the enormous amounts liberated to the environment and the ease with which the aerosol is inhaled. Patterson (1965) was the first to warn about the severity of the toxic hazards of lead in the environment. Relatively recent investigations have shown that lead inhibits the formation of the blood pigment heme by inhibiting the enzyme *delta*-aminolevulinic acid synthetase. For many years, it was widely stated by the lead industry that human blood lead levels of 100 μg per deciliter represented a "safe level" with complete freedom from toxicological effects. However, WHO (1977) in its "environmental health criteria" now considers much lower blood lead levels to be associated with a variety of human toxicoses as shown in Table 1.

Relatively recent investigations have shown that lead inhibits the formation of the blood pigment heme by inhibiting the enzyme delta-aminolevulinic acid synthetase.

Thus, the liberation of lead from automobile exhausts is now seen to be a major health hazard in areas of heavy traffic, particularly to children in which low levels of lead intoxication have been shown to result in brain damage associated with learning

Table 1. Relation of human lead levels to abnormal physiological effects[a]

Blood lead μg/dl	Physiological effects
100	Original "safe level"
60–80	Lead encephalopathy
50–70	Brain dysfunction
40–50	Peripheral neuropathy, ALA excretion, anemia
30–40	Erythrocyte ATP-ase inhibition
20–35	Free erythrocyte protoporphyria
>10	Erythrocyte ALA-D inhibition

[a] Source: World Health Organization (1977).

decrements. The EPA attempted to reduce the use of lead alkyls in gasoline for more than a decade before a schedule of complete phase out was completed in 1982.

Polychlorinated Biphenyls (PCBs)

Chlorination of biphenyl (C_6H_5-C_6H_5) produces a range of chlorinated isomers of which 224 distinct congeners are possible. The commercial compounds consist of a series of fractions identified by average chlorine content (e.g., Aroclor 1242 is 42% chlorine and averages 1% $C_{12}H_9Cl$, 16% $C_{12}H_8Cl_2$, 49% $C_{12}H_7Cl_3$, 25% $C_{12}H_6Cl_4$, 8% $C_{12}H_5Cl_5$, and 1% $C_{12}H_4Cl_6$). These PCB fractions are typically viscous oils with very low vapor pressures that, because of their high chlorine content, are relatively inert to chemical degradation. Because of their stability and lack of acute toxicity (rat oral LD_{50} for Aroclor 1242 is 8700 mg per kg), "the PCBs for many years were generally considered as safe."

PCBs were introduced commercially in 1929, and annual production in the United States was 20,786 tons in 1960 and increased to 42,527 tons by 1970 (*C&E News*). Approximately 400,000 tons was produced between 1948 and 1973, and these substances, used as fireproof hydraulic fluids, lubricants, dielectrics, plasticizers, adhesives, and printing products, became ubiquitous.

Jensen (1966) first identified PCBs as environmental pollutants in marine fish and birds by their characteristic gas-liquid chromatographic patterns. Soon it was apparent that PCB congeners that have very high lipid/water partition coefficients are readily bioconcentrated in aquatic organisms and biomagnified through food chains (Table 2). In Japan, PCB oils contaminated the human diet and produced a pathological condition called Yusho or rice oil disease. The symptomology involved darkened skin; brownish pigmentation of nails, lips, and gums; and severe acne (Goto and Higuchi 1969). PCBs are highly deleterious to mammalian reproduction; mink, *Mustela vison*, are especially sensitive as shown in Table 3 (Aulerich and Ringer 1977). PCBs were first detected in Coho salmon from the Great Lakes in 1969. Between 1972 and 1974, the average PCB concentration in fish from Lake Michigan was 10.2 ppm (range 2.1 to 18.9) (Simmons 1984). Thus, the normal mink diet of freshwater fishes is responsible for widespread reproductive failures in mink farms. Speculation

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Table 2. Partition coefficients and biomagnification of PCB congeners in laboratory model ecosystem[a]

Biphenyls	*n*-Octanol/ H_2O partition	Biomagnification in mosquito fish, *Gambusia affinis*
4-Chloro	390	480
4,4'-Dichloro	5,700	1,200
2,5,2'-Trichloro	7,800	6,400
2,5,2',5'-Tetrachloro	8,100	12,000
2,4,5,2',5'-Pentachloro	16,600	12,100
2,4,5,2',4',5'-Hexachloro	29,900	42,000
Decachloro	189,300	97,000

[a]Source: Metcalf and Lu (1978).

has suggested that the widespread bioconcentration of PCBs in fish poses a threat of extinction of all fish-eating mammals (Marquenie 1990).

Table 3. Effects of dietary PCBs on mink reproduction[a]

PCB in diet (ppm)	Offspring per female
0	6.0
1	4.3
2	0.3
5	0.0
10	0.0
15	0.0

[a]Source: Aulerich and Ringer (1977).

The threat to human health from dietary intake of PCBs is obvious. State health agencies of Michigan, Indiana, Illinois, and Wisconsin have issued a Lake Michigan sport-fish advisory that women and children should not eat lake trout 20 to 23 in. in length, Coho salmon over 26 in. chinook salmon 21 to 32 in., and brook trout up to 23 in. Fish larger than these limits should not by eaten by anyone. PCB contamination of Great Lakes fish has destroyed a $500 million commercial fishing industry.

PCB production was banned in Sweden in 1972 and discontinued in the United States in 1976. However, it is estimated that between 1930 and 1970 the total loss of PCBs in North America alone was about 500,000 tons, with 30,000 tons dispersed in air, 60,000 tons discharged into water and underlying sediments, and 30,000 tons deposited in landfills and dumps (Simmons 1984). Thus, PCB contamination of the total environment will persist for many years to come.

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Dibromochloropropane (DBCP)

1,2-Dibromo-3-chloropropane ($BrCH_2CH_2BrCH_2Cl$) bp 196°C is a soil fumigant and nematocide introduced in the United States in about 1955 and found especially useful for the control of plant parasitic nematodes that attack grapes, peaches, citrus, pineapple, and soybeans. Unlike other soil fumigants, DBCP could be safely applied to soils with growing perennial crops. Because of its high boiling point and comparatively low toxicity (rat oral LD_{50}: male 0.17 g/kg and female 0.26 g/kg), "it was considered as a very safe soil fumigant." United States production was 12 million pounds in 1976. Torkelson et al. (1961) found that laboratory rats, mice, rabbits, and guinea pigs exposed to 12 ppm DBCP vapors for 70 to 92 days exhibited severe atrophy and degeneration of the testes, which in rats was characterized as degenerative changes in the seminiferous tubules, an increase in sertoli cells, reduction in the number of sperm cells, and development of abnormal sperm cells. Rats exposed to 5 ppm DBCP had testicular weights reduced by 50%. However, it was concluded that if human worker exposure were limited to 1 ppm, "there would be little likelihood of injury." This toxicological data was submitted in 1961 to the Food and Drug Administration (FDA) and U.S. Department of Agriculture (USDA) by the manufacturers of DBCP in a peti-

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tion to establish tolerances on 44 crops. The tolerances were reviewed by FDA and USDA, and tolerances were established on food crops based on the belief that DBCP degraded in soils to produce inorganic bromide ions, which were taken up by plants. The tolerances granted ranged from 5 ppm for apricots, nectarines, and peaches to 130 ppm for endive and lettuce.

Subsequently, the National Cancer Institute published carcinogenicity studies with laboratory rats and mice (Olson et al. 1973) showing that rats and mice exposed to DBCP developed a very high incidence of gastric and mammary tumors. Although these studies were confirmed by industry carcinogenesis studies, for more than 4 years these results were not communicated to workers producing or using DBCP (Pollack 1979).

Federal regulation to severely limit the use of DBCP originated only in 1977. In that year a group of male agricultural chemical plant workers who were concerned about their inability to father children contacted an independent laboratory through their union to analyze sperm samples, after being refused help by their employer. Test results showed significant evidence of sterility. The National Institutes for Occupational Safety and Health (NIOSH) evaluated working conditions in the plant and eventually confirmed that exposure to DBCP was causing oligospermia or azoospermia. Subsequently, the EPA and the Occupational Safety and Health Association (OSHA) conducted sperm counts on several hundred male workers in South Carolina, California, and Texas exposed to DBCP. These men were exposed in various occupations from production to sales to agricultural work. There was a significant correlation between extent of use and exposure to DBCP (pound per day) and quantitative sperm count as summarized in Table 4 for the South Carolina cohort (Pollack 1979).

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At this point, production of DBCP was stopped by one large manufacturer, and EPA began the Rebuttable Presumption Against Reregistration (RPAR) process to control the use of DBCP in agriculture. Following extensive risk/benefit analysis and lengthy hearings that lasted for nearly 4 years, the use of DBCP was suspended on 19 vegetable crops and 11 tree fruits. These suspensions were challenged by the manufacturer and the agricultural industry. Subsequently, however, substantial residues of intact DBCP were found in edible fruits and vegetables, and it was further demonstrated that a large percentage of well waters from

Table 4. Correlation between use index and sperm count for South Carolina workers exposed to DBCP[a]

Occupation	Use index (lb/day)	Sperm count (10^6/ml)
Formulators (n = 8)	5,000	12.1
Custom applicators (n = 2)	345	2.7
Farmers (n = 18)	710	17.8
Farm workers (n = 12)	240	37.8
Researchers (n = 7)	10	101.5
Salesmen (n = 6)	450	73.0

[a]Source: Pollack (1979).

the San Joaquin Valley of California had demonstrable residues of DBCP. Therefore, EPA was compelled to withdraw all registrations of DBCP in 1982.

Leptophos

This organophosphorus insecticide was patented in 1969 as a replacement for DDT, especially for the control of Lepidopterous caterpillars, hence the name. Approximately 17 million pounds was sold in 50 countries between 1971 and 1976. Egypt received 6.67, Indonesia 2.08, Japan 1.83, and Guatemala 0.56 million pounds. Leptophos, O-methyl O-4-bromo-2,5-dichlorophenyl phenylphosphonothionate, is highly persistent and lipophilic (water solubility 9 ppb, m-Octanol/H_2O partition coefficient ca 2×10^6). This insecticide was shown to produce organophosphorus induced delayed neurotoxicity (OPIDN) in the hen in 1969, and these results were confirmed by WHO in 1971. OPIDN results from selective inhibition of neurotoxic esterase in the axons of the central nervous system, and as a result animals and humans exposed develop irreversible paralysis of the limbs together with bizarre mental effects (Metcalf 1982).

Massive applications of leptophos to cotton in Egypt in 1971 to control the cotton leafworm *Spodoptera littoralis* produced ascending paralysis and death in about 1300 water buffalo (Abou-Donia et al. 1974). There was also evidence of widespread human poisoning with lassitude, headache, muscarinic and epigastric symptoms, and depressed acetylcholinesterase (Hasson et al. 1978).

Despite these warnings, the effort to market leptophos on a large worldwide scale continued, and in 1974, EPA published its intent to set tolerances for leptophos of 10 ppm on lettuce and 2 ppm on tomatoes. These high residue values attested to the persistence of the insecticide.

From 1973 through 1975, a series of unusual nervous system complaints occurred among employees of a leptophos manufacturing plant in Houston, Texas. The symptoms included tingling and weakness in arms and legs, slurred speech, memory lapses, hallucinations, and paraplegia. The most severely affected workers were diagnosed by company physicians as suffering from schizophrenia, encephalitis, and multiple sclerosis (Curtis 1978). Concerns that developed among factory personnel and consulting physicians resulted in an investigation by NIOSH, and it was eventually found that 63 of 155 workers displayed neurological and performance decrements. Because of the many questions arising over continuing use of lephophos, EPA appointed an advisory committee that reported in October 1976 that leptophos was a delayed neurotoxin, having potential hazard to man from manufacturing, use, and consumption of residues on food. Before the committee report was issued, the manufacturer withdrew its U.S. registration applications on August 18, 1976.

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Pyriminil

This chemical, 4-(4-nitrophenyl)-N'-3-pyridinylmethyl)urea, was developed as a selective single-dose rodenticide effective against warfarin-resistant rats. Peardon (1974) presented the following oral LD_{50} values, purporting to demonstrate the highly selective rodenticidal qualities of pyriminil.

Test animal	LD_{50} mg/kg
Mouse	98
Norway rat	5
Roof rat	18
Cotton rat	20–60
Rabbit	300
Dog	500
Chicken	710
Cat	62
Monkey	2,000–4,000

"The very high toxicity to rats and the low toxicity to nonhuman primates suggested that pyriminil would be an effective and safe rodenticide for home use."

Pyriminil was registered as a rodenticide with EPA in 1975 as a house mouse tracking powder with 10% active ingredient (AI), a commercial rat killer with 2% AI, and a rat confection (Vacor®) with 2% AI. Pyriminil was test marketed in Korea in the mid-1970s and the manufacturer maintained that only a few incidents of poisoning associated with Vacor® treated grain had occurred. However, Lee et al. (1977) reported on 251 cases of human poisoning and a number of fatalities in Korea following accidental or suicidal ingestion of pyriminil. About 80% of the patients evidenced diabetic hyperglycemia, with massive necrosis of the islets of Langerhans of the pancreas and abnormal pathology of liver and kidney. Human poisoning from Vacor® ingestions developed in California, including those from ingestion of a new 0.5 pyriminil formulation sold "over the counter." It has become evident that pyriminil has human toxicity similar to that in the rat and can cause permanent life-long diabetes, intractable hypertension, and severe autonomic neuropathy (Pont et al. 1979). After considerable pressure from regulatory agencies, pyriminil was withdrawn from the market by the manufacturer in 1979.

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Toxaphene

The insecticide toxaphene is made by photochlorinating the bicyclic terpene camphene, from old pine stumps, to contain 67 to 69% chlorine. The product is a semicrystalline gum with an empirical formula of $C_{10}H_{10}Cl_8$. Toxaphene was introduced as an insecticide in 1947 and was widely used for the control of the cotton boll weevil, *Anthonomus grandis*. When registrations of DDT were discontinued in 1971, toxaphene became its primary replacement as the major cotton insecticide. Cumulative production and use by 1974 was estimated at about 1 billion pounds. Toxaphene was registered as an insecticide with EPA under a "grandfather clause" "with the general supposition that it was biodegradable and nonaccumulative through food chains." Knowledge of chemical composition and residue chemistry was nonexistent until modern GC-MS investigation showed that it was

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composed of at least 180 chlorinated terpenes (Holmstead et al. 1974), of which the most toxic is 2,2,5-*endo*-6-*exo*-8,9,9,10-octachlorobornane with a mouse intraperitoneal LD_{50} of 3.1 mg/kg. Toxaphene is extremely toxic to fish, producing a crippling collagen deformity at concentrations as low as 50 ppt, and is also an animal carcinogen.

Following development of GC methods for detecting toxaphene congeners, toxaphene residues were identified in Great Lakes fishes in 1979, and subsequent investigation has shown that lake trout, *Salvelinus namaycush,* from Lake Michigan contain as much as 11 ppm of the toxaphene congeners. Toxaphene residues are now known to be widespread in the Great Lakes and to be bioaccumulated through food chains (Rice and Evans 1984). Toxaphene has been widely used as an insecticide in the United States in the cotton-growing southern states, and it is evident that much of its dispersal into the northern Great Lakes has resulted from atmosphere transport and deposition. As a result of these findings, the registration of toxaphene was canceled by EPA in 1982.

Chlorofluorocarbons (CFCs)

These relatively inert gas/liquids, of which trichlorofluoromethane ($FCCl_3$) bp 23.7°C (CFC 11) and dichlorodifluoromethane (F_2CCl_2) bp 29.79°C (CFC 12) are the best known, were invented by Henne & Midgely in 1930 and found immediate use as refrigerants. Their success as propellants for aerosol sprays invented by Goodhue & Sullivan greatly accelerated usage and U.S. production of CFCs (in metric tons) rose over the years as follows:

1942	4,500
1958	60,000
1962	100,000
1970	150,000
1974	200,000

In 1972, more than 2.7 billion aerosol dispensers were produced in the United States. Production in the rest of the world equaled or surpassed U.S. production by 1974. CFCs were widely believed to be "so stable that they are entirely harmless" (*Encyclopedia Britannica* 9th ed., 1956). However, in 1974 Molina and Rowland predicted from computer modeling that CFCs released into the atmosphere slowly diffuse into the stratosphere where they undergo the following reactions with ozone, a gas that forms a barrier around Earth which protects against the passage of ultraviolet radiation.

$$CF_2Cl_2 + h\upsilon \rightarrow CF_2Cl + Cl$$

$$Cl + O_3 \rightarrow ClO + O_2$$

$$ClO + O \rightarrow Cl + O_2$$

The ClO formed can regenerate Cl by reacting with atomic oxygen. Therefore, one atom of Cl can degrade a large number of molecules of O_3. Although EPA banned the further U.S. use of CFCs as aerosol propellants in 1978, the slow diffusion rates and relative stability of these CFC molecules, together with the large reservoirs of CFCs in the stratosphere, formed the basis for a prediction that ozone levels would continue to decrease for

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another 7 to 8 years (Guttowsky 1976). The estimated atmospheric lifetime of CFC-11 is 75 years, and its concentration is 2.3×10^{-4} ppm; and that of CFC-12 is 110 years, with a concentration of 3.8×10^{-4} ppm (Hileman 1989).

Although the modeling predictions were vigorously challenged by the chemical industry, especially in developing countries, the discovery in 1985 of a large hole in the ozone layer above Antarctica has been repeatedly verified. Several international congresses have called for a total ban on the production of CFCs as the only way to prevent substantial destruction of the ozone layer. Nevertheless, by mid-1990, 15 years after the initial warning, there is still no concerted worldwide action.

It has been demonstrated that exposure to ultraviolet light of wavelengths from 280 to 320 nm is responsible for initiation of skin cancers: basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. The incidence of these neoplasms is highest in areas of intense solarization (e.g., Queensland, Australia, where it is 39.6 per 10^5 population annually and Norway where it is 12 per 10^5). In both of these areas, the incidence is doubling every decade. In Arizona, the incidence has quadrupled over the past 10 years (Rook et al. 1986). The American Cancer Society estimates that 1 in 7 Americans, or more than 600,000 in 1990, will develop skin cancers during their lives. Although skin cancers usually arise as much as 30 years after ultraviolet exposure, 25% of those currently diagnosed with malignant melanoma were under age 39. Increasing damage to the ozone layer, which protects Earth from this dangerous ultraviolet radiation will inevitably be followed by heightened incidence of skin cancer in humans.

Summary and Conclusions

Each of the seven case studies presented here relates to synthetic organic chemicals that have had extensive use and have contaminated various segments of the human environment. Each of these chemical contaminants was developed and used widely under the supposition that it was "generally regarded as safe." In every case, detailed investigations made after uses were established and markets developed have shown that these substances were so toxicologically and environmentally hazardous that they had to be withdrawn from the market place. The most sobering lessons to be learned are (1) the

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Table 5. Time required after introduction of new chemicals for warnings of hazards and for eventual regulation

Chemical	Year introduced	Warning of hazard	Decisive regulatory action
Tetraethyl lead	1922	1965	1982
PCBs	1929	1966	1976
DBCP	1955	1961	1982
Leptophos	1969	1971	1976
Pyriminil	1975	1977	1979
Toxaphene	1947	1979	1982
CFCs	1930	1974	1990

inordinate period of time required after commercial introduction of the new chemical until the first warning of toxic hazard occurred and (2) the even more astonishing lengths of time after the unmistakable warning until decisive regulatory action was taken. These dates are summarized for the seven chemicals in Table 5.

With increasing proliferation and production of synthetic organic chemicals and the exploding human population, the human inhabitants of our world can no longer afford to wait for decades to determine toxic hazards of chemicals already in use and to implement decisive regulatory action. The importance of this symposium on "Access and Use of Information Resources in Assessing Health Risks from Chemical Exposure" lies in its organization and support by the Oak Ridge National Laboratory, Biomedical and Environmental Information Analysis Section, and by the EPA Office of Health and Environmental Assessment. It must be evident that if we are to better assess health risks from chemical exposure, we need the broadest possible use of information on hazards, and if we are to minimize these hazards at an acceptable rate, we need decisive regulatory action.

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Environmental Laws Regulating Chemicals: Uses of Information in Decision Making Under Environmental Statutes

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Three areas are addressed in this paper: generic issues that arise simply in the process of decision-making under environmental statutes; different decision-making standards under various environmental statutes; and efforts to legislate a "safe" or "acceptable" risk from exposure to carcinogenic chemicals.

The scope of this paper is a rather difficult assignment — environmental laws regulating chemicals. It is roughly equivalent to being asked to explain the biology of toxic substances in half an hour. I could provide a thumb-nail sketch of a list of statutes and, along the way, bore you with a large number of acronyms that you've probably all heard before. However, I don't think that would do you any good. What I thought I would do is give you some idea about the different ways information is used under various statutes and some different ways to think about how the information you produce is used by government regulators.

There are three main areas I will address: generic issues that arise simply in the process of decision-making under environmental statutes; different decision-making standards under various environmental statutes; and finally, some issues I want to get off my chest about efforts to legislate a "safe" or "acceptable" risk from exposure to carcinogenic chemicals.

Issues in the Decision-Making Process

Several issues are involved in the process of decision-making under environmental statutes that significantly affect the way information is used by government regulators.

Several issues are involved in the process of decision-making under environmental statutes that significantly affect the way information is used by government regulators.

1. Decisions must be made.

The first and most important point to note is that when dealing with the regulation of a chemical under environmental statutes, a decision must be made. Regulators do not generally have the luxury of sitting back and waiting for more information or more studies. It is absolutely critical to remember that a decision to wait for more information is in itself a decision. In some cases, waiting for more information prevents the introduction of a new chemical into the market. In other cases, waiting may allow continued human and environmental exposure to a potentially harmful chemical. Every decision, whether to act or not to act, is a decision with important consequences.

Regulators do not generally have the luxury of sitting back and waiting for more information or more studies.

2. Decisions are almost always based on imperfect data.

Decisions involving the human and environmental effects of chemicals are almost always based on imperfect data. Indeed, a primary characteristic that unites all of the many environmental statutes, perhaps the fact which defines environmental law itself, is that decisions are made under conditions of almost complete uncertainty. Yet, this is something that regulators, lawyers, and the general public, have to live with.

As a scientist, you may be accustomed to rejecting a study because it has a p- value of 0.1, (i.e., a 10% chance that the outcome can be attributed to chance) and is therefore not statistically significant. It may be somewhat difficult to accept the fact that decisions are made and conclusions are drawn based on data that you might not feel comfortable with at all. None the less, it must be done. You use the best data that is available, and you go forward.

3. Decisions may be made using various procedures.

In some cases, decisions are made using "notice and comment" rule making. The government publishes a proposed regulation, accepts comments from the public, considers these comments, and publishes a final rule with an explanation that responds to the comments and explains the rationale for the decision. This process involves mostly written comments and written explanations. In other cases, there may be an obligation to follow almost trial like procedures that may include public hearings and cross examination of witnesses.

4. Adequacy of the data may vary based on the allocation of the burden of proof.

The "burden of proof" varies among regulatory decisions. In assessing the adequacy of data underlying a decision, the regulators may be affected by the allocation of the burden of proof. In many cases, it is the government that is required to document and justify its action. In some situations, however, it is the people affected by a decision who have the burden of proof. At least nominally, for example, if a permit is being issued, it is the proponent of the permit, that is the person seeking the permit, who has the burden of proving that the government's action was improper.

5. Courts apply varying standards of review.

There are also differences in the standards of review applied to various regulatory decisions. This means that there is some variation in how carefully a court will scrutinize a decision. In most regulations adopted through notice and comment rulemaking, the standard applied is whether the decision is "arbitrary and capricious." Under the Toxic Substance Control Act (TSCA), however, the statute specifically states that the decision has to be based on "substantial evidence." At least theoretically, the "substantial evidence" standard requires a greater burden of justification than does a standard of "arbitrary and capricious."

It may be somewhat difficult to accept the fact that decisions are made and conclusions are drawn based on data that you might not feel comfortable with.

There are differences in the standards of review applied to various regulatory decisions.

6. There is no consistency or rationality among various statutes.

Finally, do not look for any consistency or rationality among various statutes in how these various issues are parceled out. Each statute is influenced by varying political influences, and each has its own history. It is very hard to come up with explanations why, under one statute, you go through a trial-like hearing whereas under another statute you can adopt a rule by notice and comment rulemaking. There may be no rational explanation for the difference other than the evolutionary history of the particular statutes.

Varying Statutory Standards

Another basic point is that environmental statutes have different statutory standards—different goals—which means the information is used in different ways. I get uncomfortable when I see a health assessment or a health review document of a chemical prepared in the abstract. Most of the statutes are not designed to generate information; they are designed to produce action based on information. Information on health effects is used in different ways under different statutes.

I will attempt to categorize some of the different standards that are used in environmental statutes. Don't get an idea that these are hard and fast categories—they're not; they blend into one another. It is, however, useful to have some idea about the different ways in which information might be used.

1. Absolute safety

The simplest approach I will call absolute safety. Perhaps the clearest of the few examples of such a standard is the Delaney Clause in the Food, Drug and Cosmetic Act. Under this statute, for example, a food additive is classified as unsafe and prohibited if it has been determined to be a carcinogen. Statutory language, at least for food additives, is that it is unsafe if it is "found to induce cancer when ingested by man or animal or if it is found after tests which are appropriate for the evaluation of the safety of food additives to induce cancer in man or animal." This purports to demand absolute safety; nothing may be used as a food additive if it has been found, through tests, to be a carcinogen.

You may be aware that there are ways around this clause. The FDA has tried to evade or minimize the impact of the Delaney Clause through a variety of techniques. For example, they have rules relating to the sensitivity of method of the test procedures. There was also an attempt by the FDA to come up with a *de minimis* rule, which said that "insignificant" or *de minimis* levels of carcinogens or *de minimis* risk associated with carcinogens would not violate the Delaney Clause. This attempt was struck down by a court that held that Congress had specifically and clearly stated that any level of carcinogen would be considered unsafe as food additive. Thus, Delaney stands as essentially a rule of absolute safety.

2. Unreasonable risk

Another approach used in statutes requires a determination of

Do not look for any consistency or rationality among various statutes in how these various issues are parceled out.

The simplest approach I will call "absolute safety."

whether a risk is "unreasonable." Where a statute allows consideration of "reasonableness," it generally involves a balancing of economic impact with health effects. One good example is in the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA), which deals with the registration of pesticides. Under FIFRA, the EPA must consider whether the use of a pesticide will cause "unreasonable adverse effects on the environment." The definition of unreasonable risk to man or the environment "takes into account the economic, social, and environmental costs and benefits of use of the pesticide." This may involve something like a cost-benefit assessment although it is generally not a strict cost-benefit analysis. It does, however, give room to balance costs and benefits. This is in stark contrast to the Delaney Clause, which does not allow such a balancing.

Where a statute allows consideration of "reasonableness," it generally involves a balancing of economic impact with health effects.

Another characteristic of statutes that have some concept of reasonable risk is that there is almost never guidance on how to strike the balance; the agency generally has broad discretion in determining how to balance competing interests. For example, in a case involving establishing standards for allowable pesticide residues on raw agricultural products under the Food, Drug and Cosmetic Act, at one point, the agency continued a tolerance for ethylene dibromide (EDB) based on the economic impact on foreign countries if the tolerance were eliminated.

3. Environmental quality-based decisions

Under a third type of standard, decisions are made based on consideration of the effects on environmental quality or human health. The primary ambient air quality standards under the Clean Air Act [National Ambient Air Quality Standards (NAAQS)] require that the agency determine a standard based solely on the effect on human health and the environment. The statute says, for example, that "a national ambient air quality standard shall be the ambient air quality standards, the attainment and maintenance of which in the judgement of the administrator based on such criteria and allowing adequate margin of safety, are requisite to protect the public health." Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or "Superfund"), the basic standard for establishing cleanup levels at hazardous waste sites is "protection of human health and the environment." In most cases, at least nominally, environmental quality-based decisions are not supposed to involve consideration of economic impacts. Implicitly, however, this is always considered.

Decisions are made based on consideration of the effects on environmental quality or human health.

There are many familiar problems in defining an adequate, acceptable number to reflect protection of human health and the environment. This is particularly difficult to do with possible carcinogens. How is a safe level, or a level that has an ample margin of safety for protection of the environment, established? What risk constitutes an acceptable risk when you are operating on the assumption that a chemical carcinogen does not have an effect threshold? What health effects do you look at? Are you just looking at carcinogenicity or are you looking at reproductive

or behavioral impairments as well?

4. Technology-based standards

In some statutes, standards are established not on the health or environmental impact of a chemical but on the technological and economic ability of industry to control the discharge of a chemical. This is a "technology-based" standard, and such a standard essentially ducks the difficult questions of defining a safe level. Most discharge limits established under the Clean Water Act, for example, are technology based. You may have heard of best available technology (BAT) or best practicable technology (BPT) limitations. All industrial dischargers in the United States are required to meet these standards, which are based on the availability and cost of pollution control equipment.

The advantage of a technology-based standard is that it allows you to avoid the difficult decisions and the uncertainties involved in setting a health-based or environmental quality-based standard. The regulators are generally working with data, such as the costs and removal efficiency of a biological treatment system, which is more reliable and with which they are more comfortable.

There are, however, serious criticisms of technology-based standards. In general, the goal of environmental statutes is not simply the reduction of pollution, but protection of human health and the environment. Technology-based standards generally do not take into consideration, in any direct way, the impact on the environment of controlling the pollutant. This can lead to either overregulation or underregulation. A technology-based standard may reduce pollutants well below levels that will affect human health. Critics would argue that this is overregulation. In the more likely case, however, a technology-based standard may not reduce pollution enough, and people and the environment are still exposed to risk.

How is a safe level, or a level that has an ample margin of safety for protection of the environment established?

5. Communications standards

Finally, there are statutes that do not directly regulate conduct at all but which rely on communication and the dissemination of information. Perhaps the granddaddy of them all is the National Environmental Policy Act (NEPA) which requires the collection and dissemination of information through the environmental impact statement process. There is very little substance to NEPA. The U.S. Supreme Court has indicated that NEPA is purely a procedural statute that may not itself authorize the government to impose regulatory controls or alter its substantive decisions. What NEPA does do is get information out to the public and to the decision maker. Other statutes usually provide authority to take action.

There are other more current examples in which providing information is the basis for a statutory scheme. The Occupational Safety and Health Administration (OSHA) has promulgated a communications regulation that requires employers to provide workers with information about various chemicals to which they may be exposed in the workplace. The new, and already infamous, Title III of

There are serious criticisms of technology-based standards.

CERCLA contains the "community right-to-know" provision, which, among other things, requires industrial facilities to develop information both about the quantities of certain hazardous substances they release into the environment and to provide information to local emergency planning boards.

These statutes all have an interesting common objective or rationale, or at least we can provide a common rationale. Basically, it is the idea that the free market can work in environmental regulation the way it works in the marketplace. The statutes appear to assume that there will be consequences from the dissemination of information. In other words, if you get information out, action will flow. Workers, for example, will bargain for reduction of chemicals in the workplace or bargain for higher pay because of exposure. Neighbors may sue a facility for creating a nuisance.

Actually, the most important consequence of the dissemination of information under these statutes may be that it triggers political action. Congress is now in the final stages of adopting amendments to the Clean Air Act, and there are significant provisions in the proposed amendments dealing with toxic emissions from industrial facilities. One of the driving factors has been recent information about toxic emissions that is based on information required by statutes.

There is a quote relevant to these information statutes and relevant to the work a lot of you do. Justice Louis Brandeis thought that the free exchange of ideas would protect against private corruption. He wrote "sunlight is the best disinfectant," and it seems to me to be a nice quote for toxicologists involved in information dissemination.

Problems in establishing "acceptable" levels of risk

Finally, let me leave you with something that I have been wanting to get off my chest. There is a lot of talk among agencies and in Congress about coming up with a magic number to define negligible risks or acceptable risks. The idea is that, through risk assessments, we can come up with fairly good estimates of risks to human health and that we can use this information to define some safe or acceptable level of risk. These days the commonly advocated "safe" levels involve risks ranging from one in ten thousand to one in a million. I have some trouble with this approach, and I just wanted to share my concerns with you and stimulate your thinking about it. There are two reasons that I think it may not be appropriate to define "the" safe level of exposure.

1. Not all risk assessments are conservative.

The first of these involves the common, and I believe, erroneous belief that all risk assessments are based on conservative assumptions and always overstate risks. EPA has said this, and certainly industry likes to point out the conservative assumptions that are used in the extrapolations from mice to humans.

I don't know how many of you believe this, but, if nothing else, the history of establishing estimates of safety for various

OSHA has promulgated a communications regulation that requires employers to provide workers with information about various chemicals to which they may be exposed in the workplace.

The most important consequence of the dissemination of information under these statutes may be that it triggers political action.

chemicals should put you on guard. Let me point out just two areas in which the assumptions may not be so conservative. Risk assessments involve not only judgements of the potency or dose response for a chemical but also exposure assessments. In the Water Quality Criteria, for example, exposure assessments used to be, and I think still are, based on an assumption of exposure of a 70-kg human, drinking 2l of water and eating 2g of fish per day over a 70-year lifetime. I exceed the 70-kg standard, but many other people do not. You will note, for example, that women and children are not particularly well represented. Another problem that has troubled me is that the exposure does not include anything other than oral exposure. I have not seen many risk assessments that include estimates of exposure by dermal contact, and yet it is obvious that for some chemicals, dermal contact through a shower can result in as much of a chemical entering the body as by drinking the water.

Another "nonconservative" assumption involves the end point of concern. For most of the controversial chemicals, cancer is the concern. Although there may be questions about the adequacy of the data on carcinogenicity, frequently there is no data on neurological or reproductive effects which may occur over a broad exposure range. This lack of data is frequently lost in the shuffle when regulatory numbers are produced based on potential carcinogenic effects. Additionally, the assessment may not be considering environmental effects; be careful to identify what end point was observed in a risk assessment.

2. Not all risks are equally acceptable.

A second reason that I'm uncomfortable with using risk assessment to establish a level of "acceptable risk" is that I am simply not sure what having one specific number to indicate acceptable risk means.

A troubling problem is that the exposure does not include anything other than oral exposure.

Some researchers have reviewed the risks that are accepted by the public in a range of activities to define a single "acceptable" level of risk. However, not all risks are created equal. I may be willing to accept a 10^{-4} risk to have gasoline to drive my car. I may not be willing to accept the same risk in order to get a fluorocarbon to spray *Pam* on pans to stop food from sticking. A one-in-a-million risk may be very low, but I may not be willing to accept even that level if it is for an activity that I think is essentially frivolous or not beneficial.

I think there is an allure in picking a specific number that ignores the fact that almost everything is going to involve a trade-off. I worry that we lose some of the appropriate information and cut off the regulation process if we define a specific risk level. In fact, the only rationale that I can think of for coming up with a specific number is to eliminate certain transaction costs. It avoids the expense of acquiring additional data about costs and benefits. This may or may not be an adequate justification. Keep in the back of your mind, though, that the issue of what is an acceptable risk level is not in any sense a factual question about the risks we accept when

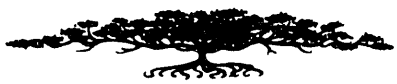
Another "nonconservative" assumption involves the end point of concern.

undertaking other activities, such as driving a car. It is a question about how much we are going to pay to get more information about the costs and benefits of the activity being regulated. If that is the case, it really requires a case-by-case decision based on the activity that is being regulated.

Conclusion

Environmental statutes use information about the environment in a variety of ways, and the data you generate are going to be plugged in and distorted and twisted and used in a variety of different contexts. You should recognize that after data leaves your hands, there is a whole new process, with its own constraints and problems, that goes on before final decisions are made.

Not all risks are created equal.



Information Needs for Risk Assessment

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Risk assessment can be thought of as a conceptual approach to bridge the gap between the available data and the ultimate goal of characterizing the risk or hazard associated with a particular environmental problem. To lend consistency to and to promote quality in the process, the U.S. Environmental Protection Agency (EPA) published Guidelines for Risk Assessment of Carcinogenicity, Developmental Toxicity, Germ Cell Mutagenicity and Exposure Assessment, and Risk Assessment of Chemical Mixtures. The guidelines provide a framework for organizing the information, evaluating data, and for carrying out the risk assessment in a scientifically plausible manner. In the absence of sufficient scientific information or when abundant data are available, the guidelines provide alternative methodologies that can be employed in the risk assessment.

Introduction

The purpose of this paper is to outline and describe some of the information needs of risk assessors within the context of both the risk assessment process and the EPA guidelines. Risk assessment can be thought of as a process to bridge the gap between the available data and the ultimate goal of characterizing the risk or hazard associated with a particular environmental problem. To lend consistency to and to promote quality in the process, the EPA published Guidelines for Risk Assessment of Carcinogenicity, Developmental Toxicity, Germ Cell Mutagenicity and Exposure Assessment, and Risk Assessment of Chemical Mixtures. The guidelines are intended to be a dynamic blueprint to guide the risk assessment process from experimental data to risk characterization. The guidelines provide a means for directing the thought process for organizing the information, evaluating data, and carrying out the risk assessment. The guidelines also direct presentation of a meaningful synthesis of the information (risk characterization) that clearly calls out all of the limitations associated with the risk assessment process.

Guidelines provide a means for directing the thought process for organizing the information, evaluating data, and carrying out the risk assessment.

In assessing information needs for any risk assessment, several variables must be addressed. One factor to be considered is the specific issue being addressed or the goal of the risk assessment. Risk assessment can have many applications such as risk screening and setting time or resource-based priorities, in addition to more traditional approaches. Typically, risk assessment defines the basis for regulatory action in terms of setting standards or defining criteria or remedial action. It is obvious that the latter goal can be met only with a more data-intensive risk assessment process than would be used for priority setting. Another factor in defining information needs is the time frame available for completion of the assessment process. A short time span will certainly circumscribe the scope of a risk assessment process and the attendant data-gathering

Risk assessment defines the basis for regulatory action in terms of setting standards or defining criteria or remedial action.

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effort. It is not unusual to encounter circumstances in an EPA regional or state office in which an immediate turnaround is needed. On the other hand, a regulatory action can sometimes span not just years but decades, depending on the immediacy or perceived immediacy of the problem.

In a rather circular fashion, the use of risk assessment methodologies or tools is limited by the data available, and the information needs are defined by the choice of a risk assessment methodology. Some methods are obviously much more data intensive than others. For example, the multistage model used for quantitative risk estimates for nonthreshold responses (such as cancer induction) requires the incidence data. Many exposure assessment tools and models require specific types of data, such as population size, location, food sources, and so on. The key is to match models and methods to the data available. The EPA guidelines facilitate that process by delineating procedures for data choice, thereby defining what data can be used for the specific type of risk assessment (i.e., the kinds of assays and data that are, in fact, suitable for use).

Still another consideration is the audience for the risk assessment. Although consideration of the target audience may not influence the risk assessment process, it should affect the presentation of the information. In some cases, especially when a nontechnical group is to be the recipient of information, it may not be necessary to provide details of models, lengthy descriptions of experimental assays, and so forth. It is important, however, to convey a sense of the extent (or lack) of data used in the estimate as well as the assumptions used and uncertainties involved. The Risk Assessment Guidelines provide a framework for defining uncertainties in the process and specify the use of default values for procedures to be used in the absence of information. Risk communication must be done so that the audience is informed rather than confused or misled. An example of documents that are aimed at both risk professionals and the general public are the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles. These documents begin with a general public health summary, written in jargon-free language, of health effects that might be encountered in exposed human populations. This is followed by a more technical description of data and risk assessment.

Use of risk assessment methodologies or tools is limited by the data available, and the information needs are defined by the choice of a risk assessment methodology.

Risk Assessment Process as a Determinant of Information Needs

At this time, the EPA has guidelines only for risk assessment regarding the identification and characterization of adverse health effects linked to human exposure. As described by the National Research Council (NRC 1983), risk assessment consists of four interrelated components: hazard identification, dose-response assessment, exposure assessment, and risk characterization (Fig. 1). The first component of the risk assessment process is hazard identification, which is a qualitative index of the nature of the effects and their biological significance. The

An example of documents that are aimed at both risk professionals and the general public are the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles.

major question to be answered in the hazard identification step is the likelihood that effects observed in one population (usually experimental) could occur in another population (usually human). Several issues are linked to hazard identification. The first is the validity and the meaning of the toxicity data. Not all data are created equal, hence, data should be evaluated for their legitimacy in terms of the risk assessment process. It's clear that technology has become increasingly sophisticated in its ability to detect effects; what has not kept pace is the risk assessor's ability to interpret the biological significance of those effects.

One process for organizing hazard data and presenting conclusions is the weight-of-evidence (WOE) scheme. The most widely used weight-of-evidence classifications have been developed to assess the likelihood of a material to be a human carcinogen. EPA currently uses a carcinogen classification process similar to that developed by the International Agency for Research on Cancer (IARC). In this system, human data and that derived from animal bioassays are evaluated on whether they constitute sufficient, limited, inadequate, or no evidence for carcinogenicity. After a preliminary classification has been established, data on metabolism, genotoxicity, and other mechanistic data are considered in arriving at final classification. The EPA also employs WOE schemes in the processes of hazard identification of human germ cell mutagens and developmental toxicants. Criteria for all of the WOE judgments are described in the Risk Assessment Guidelines.

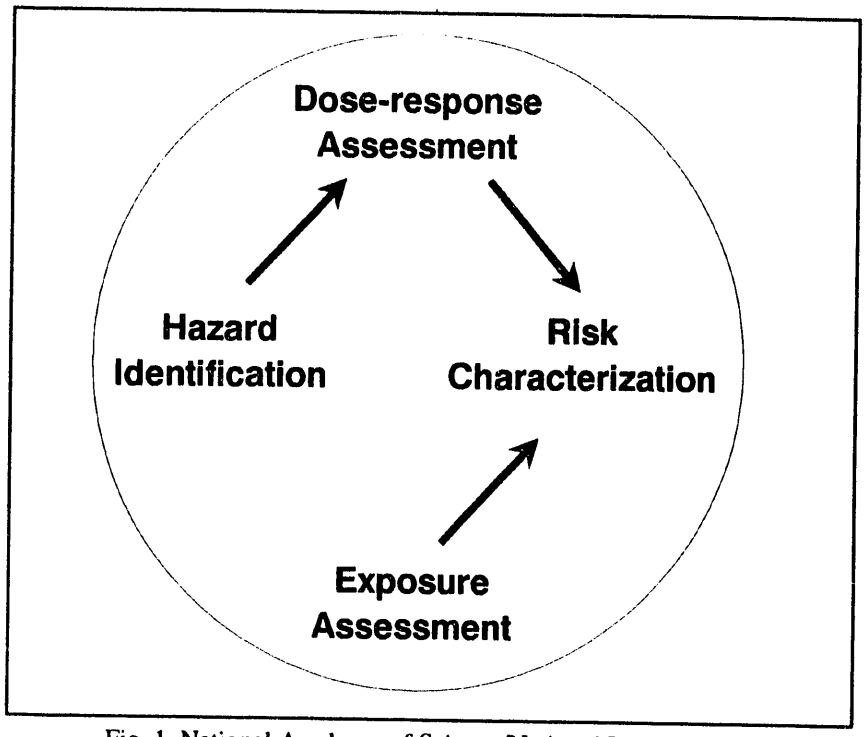

Fig. 1. National Academy of Science/National Research Council risk assessment paradigm.

All have procedures in common for (1) evaluating data for its appropriateness to the risk assessment, (2) describing minimal data requirements, and (3) organizing the data.

The second component of risk assessment is the dose-response assessment, which is evaluation between dose and some measured response. Usually, the only data available to the risk assessor are from animal assays using relatively high doses or epidemiologic data from humans exposed to high concentrations in the work place or by some accidental means. However, the job of the assessor of environmental risks is to estimate the magnitude of expected health consequences from ambient exposures. Figure 2 illustrates the chief difficulty in this task, that of inferring the shape of a dose-response curve at exposures below the experimentally

The second component of risk assessment is the dose-response assessment.

observed range. Such inferences are the source of significant uncertainty. Information needs are driven by the uncertainty recognized in the risk assessment process. The most useful, and least common, type of information is incidence of observed effects at doses approximating the expected exposure to humans. The EPA guidelines provide assistance in choosing models for extrapolation to low doses for less-than-ideal data. This includes judgments as to the actuality (or at least to the statistical significance) of an apparent dose-response relationship and the use of information regarding the mechanism of toxicity in the choice of a low-dose extrapolation procedure. For example, the guidelines support the use of an extrapolation procedure that incorporates low-dose linearity for presumed carcinogens, based on hypotheses wherein a carcinogen initiates the carcinogenic process through an irreversible change in the cellular DNA. This hypothesis is supported in general for a number of chemicals by a large body of data; information on the mechanism of carcinogenicity for the chemical in question removes more of the uncertainty in the application of a linear low-dose model. The guidelines further specify that unless data exist to recommend a particular model, the linearized multistage model be used. This model, as any other, has specific data requirements: there must be numerical incidence data, a single number (as opposed to a range) must be used for dose, and there must be at least two dose groups (one of which must be nonzero).

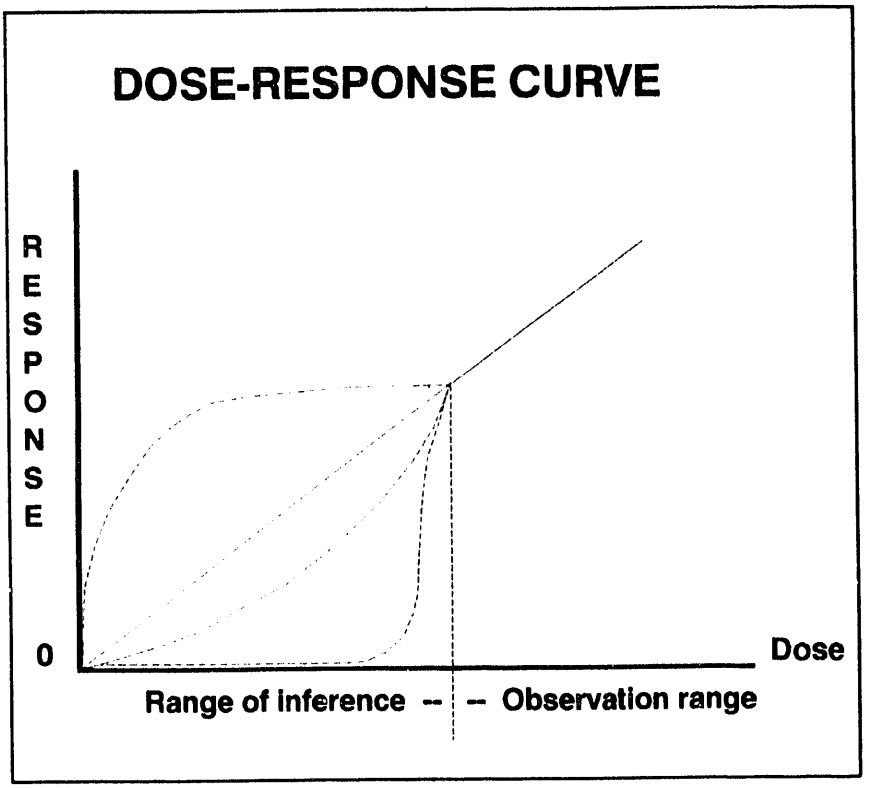

Fig. 2. Inferring the shape of a dose response curve at exposures below the experimentally observed range.

The third component of the risk assessment process is exposure assessment. This step attempts to determine whether the impact or the target of the hazard could be a population or a specific subpopulation. Exposure assessment also addresses the pathway, or pathways, by which the agent reaches that target. The issues in exposure assessment include the most likely route of exposure (dermal, inhalation, or oral); the nature and identification of the exposed population; and the magnitude, duration, and frequency of exposure. Built into this process is consideration of the events and the properties and characteristics of the populations that might potentiate or mitigate concern about defined risks.

The third component of the risk assessment process is exposure assessment.

The risk characterization component requires increasingly greater attention in the risk assessment

community. This component is an attempt to integrate hazard identification, dose response assessment, and the exposure assessment into qualitative or quantitative assessment. A challenge in risk characterization is that these different components of the risk assessment process are often carried out by distinctly different groups of scientists or disciplines, and very often the uncertainties linked to each of the components in the process are lost as the conclusions are carried forward to the risk characterization stage. The challenge is to tighten the linkage between these components of the process so that the risk characterization is the most biologically plausible characterization that can be developed, while identifying the uncertainties inherent in the process.

Clearly, the use of animal data raises the question of concordance of effects among species, especially in light of "negative" epidemiologic studies. Concerns about factors, links to epidemiological studies, and the difficulty in accurately quantifying the exposures are often linked to these studies. Extrapolation of high to low dose and extrapolation from animals to humans in a quantitative sense are concerns in the dose response assessment. The degree of confidence increases when the approach is adjusted from modeling to ambient monitoring to biological monitoring. The presentation of the risk characterization presents the opportunity for a comprehensive discussion of the uncertainties encountered and assumptions used in the risk assessment process.

Examples of Effect of Information Availability on Risk Assessment

The degree to which the extent and type of data available influences the methods and processes of risk assessment is illustrated in this section. It uses chronic noncancer health risk assessment as an example.

The degree to which the extent and type of data available influences the methods and processes of risk assessment is illustrated.

The Reference Dose (RfD) (formerly called the Acceptable Daily Intake) continues to be the foundation of risk assessment for noncancer end points despite occasional flurries of criticism. RfD is defined as an estimate spanning an order of magnitude that is likely to be without adverse health effects or significant risks to human populations over a lifetime of exposure. Procedurally, the development of RfD is very straightforward:

$$RfD = \frac{NOAEL}{UF \times MF}$$

where

NOAEL = No-Observed-Adverse-Effect Level

UF = Uncertainty Factor

MF = Modifying Factor

The NOAEL is generally derived from experimental animal data but may be based on human data. The magnitude of the uncertainty factor and the modifying factor is inversely proportional to the confidence in the database and directly proportional to the need for additional or better types of information. "Better types of information" does not necessarily refer to value judgements about the conduct of studies but to studies that are most relevant to the risk assessment process.

The NOAEL is generally derived from experimental animal data but may be based on human data.

The risk assessment process itself will determine what types of data are sought and what types of data are, in fact, most relevant. Although the development of an RfD is operationally very straightforward, some of the deliberative factors linked to the development of an RfD are not. This is illustrated in Fig. 3, which shows a family of dose-response curves based on hypothetical animal data for biological effects of a particular agent. Liver damage linked to a NOAEL is an effect level but is construed as being nonadverse. The line representing decrease in weight gain, which is judged to be a No Observed Effect Level (NOEL) is at the lower-most portion of the curve. For the purposes of risk assessment, the point that represents a minimal amount of liver damage, but not sufficient damage to be construed as adverse, would probably be selected. Once that selection has been made, the NOAEL is scaled by application of the uncertainty factor and modifying factor magnitudes, which are a direct function of the information needs.

Table 1 shows data for the critical effect of nitrate as an example of a case in which data are not abundant, but what data does exist are very relevant. These data are for the critical effect in a sensitive subgroup—increased levels of methemoglobinemia in infants who were given formula made from nitrate-contaminated well water.

In this case, there is high confidence that we have identified the true population threshold for adverse effects (i.e., 11 to 20 ppm), which is defined as a

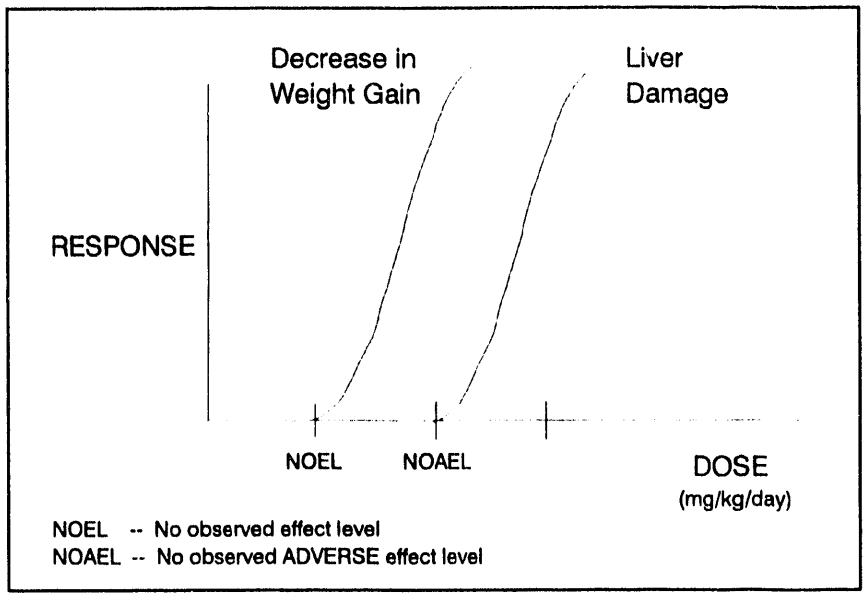

Fig. 3. Hypothetical dose-response relationships for a population.

NOEL. In this instance, the uncertainty factor is equal to 1, indicating that uncertainty around the RfD is negligible. Thus, for nitrate there exists very relevant data for human risk assessment and the information needs here are considered largely satisfied. A contrasting example is the pesticide, mirex. Mirex at one time was used in the eradication of fire ants. It was introduced into the environment in

Table 1. RfD for Nitrate

Critical effect	Experimental doses	UF	MF	RfD
Methemoglobinemia	NOEL: 10 ppm of drinking water or 10 mg/L converted to 1.0 mg/kg/day	1	1	1E+0 mg/kg/day
Infant chronic exposure to drinking water				

substantial quantities and there is an abundance of animal data on it. However these data are not as relevant to human risk assessment for a chronic exposure as are the nitrate data. The majority of the data were from studies of relatively short duration for which only frank effects were observed. The current RfD methodology requires a NOAEL, or failing that, a Lowest Observed Adverse Effect Level (LOAEL). A Frank Effect Level in animals is considered to be so far above the theoretical human threshold of effect that its use is contraindicated. The only suitable data for mirex are from a less-than-lifetime study wherein a Lowest Effect Level (LEL) was determined. This is an instance in which the information needs for risk estimation were only minimally met, thus enduring a large degree of uncertainty in the assessment, as seen in Table 2. This is reflected in the composite uncertainty factor of 10,000 — 10 each for protection of sensitive human subpopulations and animal-to-human extrapolation and an additional 100 to account for subchronic to chronic extrapolation, use of an LEL in the absence of a NOAEL, and the insufficiency of the database for determining the most sensitive toxicologic end point.

In these two examples, the risk assessment process was essentially driven by information availability (or lack thereof). In both cases, sufficient data existed to allow application of the standard RfD methodology and the provision of a risk assessment considered protective in terms of human health. For mirex, the information requirements were barely met; for other environmental agents even minimal relevant data may not be available. For example, the RfD Work Group recently considered the databases for several polycyclic aromatic hydrocarbons (PAHs) including acenaphthylene. This PAH was the subject of a 90-day gavage study in rats. Effects considered to be adverse were observed at the lowest dose tested (100 mg/kg/day). Because high mortality was observed in the female rats treated at this dose, the data were considered inappropriate for calculating an RfD. The best one could do with these data would be in preparation of a hazard screen or ranking method.

By contrast, information is abundant (approaching an embarrass-

In the examples, the risk assessment process was essentially driven by the information availability (or lack thereof).

Table 2. RfD for Mirex

Critical effect	Experimental doses	UF	MF	RfD
Decreased pup survival in a Multigeneration vole reproduction study	NOEL: None LEL: 0.1 ppm (0.015 mg/kg/day)	10,000	1	2E-6 mg/kg/day

Source: Shannon (1976).

ment of riches) in terms of useful data for risk assessment of lead. The database, in general, is sufficiently complete to the extent that it dictates a departure from the traditional reference dose approach. Because the dose response function extends to the lowest blood levels of lead identified in study populations, a discernable threshold has not been demonstrated. We also have the situation of multimedia exposures, which recognizes that the primary source of lead exposure from anthropogenic releases is the air, but oral exposure predominates. Consequently, we have to reflect multimedia exposure, reference doses or reference concentrations. In the case of lead, a powerful predictive tool is available to us, and the data required is written for its application. It has long been recognized that overt lead toxicity was associated with blood levels exceeding 30 µg/dL; impaired nervous system function, renal dysfunction, and cardiovascular system effects are all noted at these levels. However, attention is increasingly focused on subtle biochemical and neurobehavioral lesions that extend to the lowest levels of blood lead tested, which include indicators such as elevated levels of aminolevulenic acid. In adults, elevated blood pressure can be a concern because the doubling of blood lead levels from 7 to 14 mg/dL is associated with 2- to 3-mm increases in blood pressure. The question is, What is the significance of a 2- to 3-mm increase in blood pressure? Because of lead's presence in food, water, and soil, the predominant route of exposure for environmental lead is oral. The Biokinetic Uptake model, developed by Harley and Kneip at New York University and elaborated on by Jeff Cohen, formerly of the Office of Air Quality Planning and Standards, and others at Research Triangle Park (EPA 1986), describes the pharmacokinetics of lead within the body. This model has been integrated into a software package that allows the user to present health consequences of lead exposure within a context to make judgments without resorting to a single level of exposure. Using this approach, the user can integrate dose response assessment developed for health effects with the exposure assessment in the Biokinetic Uptake model to define the implications of blood lead in an exposed sensitive population, such as 2-year-old children, who are especially vulnerable because of their behavior. In this case, rather than defining a single level, one can define the population that is above a prescribed blood level. It is important to remember that several assumptions are linked to these conclusions. Most noteworthy in this case is the presumed contributions of dietary lead to overall lead exposures. The most recent Food and Drug Administration survey indicated that these blood levels might be inflated. The model now is being revised to reflect this new information.

This discussion does not suggest that the RfD is in error or has outlived its usefulness; it continues to be a very useful risk assessment tool or reference point in decision making. However, it is important to recognize that there is no single correct method for characterizing risk. Rather, decision-analytic tiers made up

Information is abundant (approaching an embarrassment of riches) in terms of useful data for risk assessment of lead.

In the case of lead, a powerful predictive tool is available to us, and the data required is written for its application.

of several methods are to be invoked, depending on data availability and the actual purpose of the assessment (i.e., for screening, ranking, prioritizing or for providing effective [predictive] estimates or conservative [protective] estimates of relative risks). A goal of a wide range of methods development and research efforts is to identify more predictive methods. These methods should represent integration of exposure and effect and be able to provide estimates of population distribution linked to body burdens and associated effects. This is heavily dependent on the aggregation of more data of many sorts, including information on mechanism of toxicity, shapes of dose response curves, toxicokinetics, and so on. This suggests the need for more useful insights regarding the appropriate use of biomarkers and of exposure, effect, and susceptibility data. Again, this would have to be tied to the development of selection criteria for the goals of a particular assessment effort, whether screening, protective, or predictive, and type of data and tools available for the characterization process. A final consideration beyond the immediate information needs already discussed would be an examination of the risk assessment process *per se* and how information databases might be used more effectively to identify recurring patterns or trends that, in turn, lend themselves to hypotheses and hypothesis testing. In this way, a new generation of risk assessment tools may emerge that extend beyond what is sometimes viewed as dichotomous safe versus nonsafe characterization of risk. It is by defining these types of issues more fully in risk characterization that we set the stage for more informed risk management decisions that incorporate social, legal, economic, and political concerns.

A new generation of risk assessment tools may emerge that extends beyond what is sometimes viewed as dichotomous safe versus nonsafe characterization of risk.

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Information Needs for Risk Management/ Communication

David A. Bennett, U.S. Environmental Protection Agency

The hazardous waste cleanup program under the Comprehensive Environmental Response, Compensation, and Liability Act (Superfund) is delegated to the ten Regions of the U.S. Environmental Protection Agency (EPA) and has, to date, identified more than 33,000 sites for consideration. The size and complexity of the program places great demands on those who would provide information to achieve national consistency in application of risk assessment while meeting site-specific needs for risk management and risk communication.

Introduction

The topic to discuss in this paper is extremely broad. It can be narrowed somewhat by relying on the perspective of the Superfund program for hazardous waste cleanup under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Superfund is a regionally delegated program, and the sites are found across the country. That in itself is a risk communications problem. Superfund is doing its share of risk management. More than 31,000 sites have been looked at nationwide, and to date, about 1200 of these have been determined to need detailed assessment and a formal risk management decision, a Record of Decision. Each site presents unique management and communication challenges. A strength of the Superfund program is that we treat each site individually. At the same time, we strive for consistency in management of the program across the country.

The goals of this paper are to review the Superfund process and opportunities for applying health risk information to management and communication. It will look at some challenges and intentions in using risk assessment in a program such as Superfund. Finally, it will identify the audiences to whom we must communicate and look a bit at the information they may request.

Goals are to review the Superfund process and opportunities for applying health risk information to management and communication.

Overview of the Superfund Program

Since the passage of CERCLA ten years ago, more than 33,000 sites that may need attention under the Superfund program have been identified and entered into a data base, CERCLIS. The preremedial program gives each of these a Preliminary Assessment based on existing information. To date, we have looked at about 31,000 of these sites and have determined that about 17,000 need additional sampling, additional assessment, and analysis — the Site Inspection (SI). The more than 13,000 SIs that have been done have produced the following results: almost 6000 sites required no further federal action, the decision process is incomplete on about 5500 sites, and about 1200 sites were

Since the passage of CERCLA ten years ago, more than 33,000 sites have been identified that may need attention under the Superfund program.

placed on the National Priorities List (NPL). The Hazard Ranking System, a structured value model using risk-based information, determines which sites pose sufficient threat to warrant further federal action and placement of the site on the NPL.

Sites on the NPL move into the remedial process for more thorough characterization, baseline risk assessment, evaluation for cleanup alternatives, and the Record of Decision. The baseline risk assessment answers two questions: How bad is this site? and, How bad could it become if we did nothing else? It considers current uses of the site and possible future uses (e.g., what would be the risk to people who moved to the site?). Risk analysis beyond the baseline may look at the remedial alternatives to ask: What will be the result of the remedial action? How can we decide 'how clean is clean' if we decide to take action? Answers to the questions must be meaningful to both risk managers (federal and state employees who are usually not risk assessors) and the public.

CERCLA directs that we design cleanup to meet standards set by other state or federal laws, so-called Applicable or Relevant and Appropriate Requirements (ARARs). Also, as a matter of policy, EPA has chosen to use risk assessment to evaluate protection of public health and the environment. This is the approach recommended by the National Academy of Sciences in 1983. The challenge for Superfund, however, is to apply it to sites that are heterogeneous, and that may have several chemicals and several pathways of exposure to populations at or near the sites. Data may be complete or somewhat incomplete, and we may not have toxicity data of high quality for all of the chemicals at the site. What we are trying to do is be responsibly, rationally conservative in the application of risk assessment to the site.

As a matter of policy, EPA has chosen to use risk assessment to evaluate protection of public health and the environment.

Some of the challenges or tensions in using risk assessment and risk information in the Superfund program include the following:

1. There is a need to act now. Congress and the public expect expeditious cleanup of Superfund sites. We cannot wait a long time for significantly better science.
2. There is the tension between doing a site-specific risk assessment that is true to the site and the perception that national consistency requires a single set of numbers or standards for cleanup levels. Superfund uses a standard process to gain the benefits of characterizing the risk and uncertainty at each site.
3. There is a tension to provide early cleanup targets to expedite engineering evaluations *vs* creating false expectations about where we might finally end up following baseline risk assessment and setting cleanup goals.
4. Finally, there is a tension between setting goals in the Record of Decision and the engineering realities of the site. When we get out there and start moving the dirt around or pumping and treating the water, realities may not quite match with the expectations—the goals. In the end, though,

There are many challenges or tensions in using risk assessment and risk information in the Superfund program.

risk analysis and comparison with goals can show that you have cleaned up the site. This is the 'how clean is clean' decision.

Audiences

Who are our audiences in the Superfund program?

Who are our audiences in the Superfund program? First, the managers. At each site there is a Remedial Project Manager responsible for that site. (S)he has to deal with the engineers, hydrogeologists, toxicologists, the people around the site, and senior management. (S)he wants to have some specific risk information to support decisions.

Another audience is the risk assessors, the toxicologists who must conduct the site-specific risk assessment. To evaluate exposures they need data that is gathered on site. To support the risk assessors' needs we have educated the people who gather data not just to look at dirt, air, and water; we look at the activities of the individuals at the site. People fish, and they eat the fish. They grow crops. (Although it is not a topic of this paper, we also look for exposures that may pose ecological risks.)

Risk assessors also need high quality, consistent sources of information on toxicity of contaminants. We take advantage of what the EPA has already done in evaluating the available toxicological information. We refer to the EPA's Integrated Risk Information System (IRIS) as the gold standard of the Superfund program. To supplement IRIS we've worked with the Environmental Criteria and Assessment Office (ECAO) of the Office of Research and Development to develop the Health Effects Assessment Summary Tables, which are published quarterly. Additional help comes from a Superfund Technical Support Center and hotline at ECAO to provide information to risk assessors when they have trouble finding sufficient information or have uncertainty about how to proceed in the Superfund program.

Engineers constitute another audience. These typically are contractors to EPA or to Potentially Responsible Parties.

The site decision-makers themselves, the managers in the Regional EPA office, are an audience.

Finally, the concerned public around the site is an audience. There is often more than one type or group who represent the concerns of the site. Many of these sites have long histories. People have been living with, on, or near these areas for sometimes many, many years. As Peter Sandman has said, many of these people are outraged. Coming to them and saying, "I'm from Washington, I'm here to help, and I've got the answer to your problem" does not deal with outrage. At some of these locations there are others who owe their jobs to the potentially responsible parties.

What information is needed for risk communication?

What do those folks want in terms of risk communication, in terms of information? The answer is "a lot of things," but there are a couple, at least, that ought to be kept in mind as we think about information sources and how they might be made available, either directly or through others, to these individuals. First, very simply, they want recognition and consideration of their concerns. A

group may have a strong, firm belief that there is a very high incidence of a particular adverse effect in the community around the site. To the toxicologist or epidemiologist there may seem that there is no evidence for the effect, at least at first view, but it can still be addressed and looked at as we do the assessment. Out of that we may find some things that we can actually do during our risk management actions, and, if nothing else, we have recognized and given consideration to the people's concerns.

The public also may want all problems removed. This is the NIMBY, not in my back yard, phenomenon that so often appears during discussion of siting a new incinerator or other facility. Superfund sees the other side of this argument: if you have lived with a problem all this time, you don't want it in your backyard any longer. However, when we are successful in communicating and providing information that is meaningful to all parties at a site, we can often form a true partnership in the decision-making process and decisions for effective treatment of wastes to minimize risks can be made.

Conclusions

For the future, I think we will see more focus on the public around sites and perhaps less on the technical details of what we do. Appropriate decisions at Superfund sites can be achieved by working with the concerned people at the sites. One example is that of EPA risk assessors and EPA site managers working with the public early in the process. Also, the Agency for Toxic Substances and Disease Registry, which must do a Health Assessment at each Superfund site, is visiting communities and state and local health departments to see what data may be available and what concerns are expressed by the people in the community. Finally, I think we'll see more information sharing among all parties, working toward more of a partnership in the program.

We need more focus on the public around sites and perhaps less on the technical details of what we do.

Evolution of Toxicology Information Systems

John S. Wassom and Po-Yung Lu, Oak Ridge National Laboratory

Society today is faced with new health risk situations that have been brought about by recent scientific and technical advances. Federal and state governments are required to assess the many potential health risks to exposed populations from the products (chemicals) and by-products (pollutants) of these advances. Because a sound analysis of any potential health risk should be based on the use of relevant information, it behooves those individuals responsible for making the risk assessments to know where to obtain needed information. This paper reviews the origins of toxicology information systems and explores the specialized information center concept that was proposed in 1963 as a means of providing ready access to scientific and technical information. As a means of illustrating this concept, the operation of one specialized information center (the Environmental Mutagen Information Center at Oak Ridge National Laboratory) will be discussed. Insights into how toxicological information resources came into being, their design and makeup, will be of value to those seeking to acquire information for risk assessment purposes.

Introduction

Scientific and technological developments have brought unprecedented benefits to our standard of living, but also have brought unprecedented problems. In an attempt to stem the tide of environmental degradation, federal and state governments now are required to provide hazard assessments and/or health risk projections for a variety of chemical agents that may have serious far-reaching consequences. To make sound and efficient assessments, the availability and use of reliable data is an essential of the risk assessment process.

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The end product of scientific research and development is new data and information. In the field of toxicology, new data and information are being generated at a phenomenal pace and are being published at an exponential rate. Much of the information published is stored in computers in one form or another for subsequent use and analysis. This situation provides both an invaluable resource and an enormous challenge to those involved in assessing health risks from chemical exposure. With large amounts of government funds being devoted to health and environmental research programs and with maintenance of our living environment at stake, the growth rate of the toxicology literature is expected to increase every year.

To cope with this growing body of literature and to make it easily accessible to users, different types of information systems have been created. Perceptions vary about how information should be handled or processed, and these differences of opinion have influenced the availability, accuracy, and use of toxicology information. Many information systems developed to serve the field of toxicology have changed significantly over the years. Several factors have served as catalysts for the changes in the systems and in how toxicology information is handled. Among these factors are different viewpoints on (1) how scientific information should be packaged for public use, (2) economic trends, and (3) research emphasis. This paper examines the evolution of

Several factors have served as catalysts for the changes in the systems and in how toxicology information is handled.

toxicology information systems in relation to current needs for ready access to reliable information to be used to identify chemical hazards and make risk characterizations.

Origins

In keeping with the evolutionary theme, we would like to quote the person who has had the most profound effect on the way we think about evolution. Charles Darwin, in his provocative book published in 1859, made a beautiful and often-quoted statement at the conclusion of his treatise regarding the origin of species: "There is grandeur in this view of life . . . From so simple a beginning, endless forms most beautiful and most wonderful have been and are being evolved" (Darwin 1859).

In the context of toxicology information centers, we have paraphrased Mr. Darwin's classic statement, "There is grandeur in this view of information systems . . . From so simple a beginning, endless forms to serve the toxicology research area have resulted—some most interesting and some most useful have been and are being evolved."

The first toxicology information system was created the moment someone filed an item of information regarding some parameter of toxicity for future reference and use. When the printing press revolutionized the production and access of written manuscripts, the volume of information increased, and files of documents were compiled and stored for future use. This particular information collection scenario was occurring in many locations throughout the civilized world as people enamored with scholarly pursuits and curiosity increased attempts to determine the toxic properties of agents of all kinds. Aside from the filing of toxicology manuscripts in personal files, collections of these documents were being housed in museums, later called libraries. Because humans have an innate need to communicate and share knowledge, early toxicologists were eager to share information and discuss their research. Investigators began to communicate with each other both in writing and in conversation, spawning the appearance of journals and specialty books oriented toward toxicological sciences. It soon ensued that among the priorities of an early scientist was the acquisition, application, and communication of knowledge. As years passed the number of scientists conducting toxicological research increased as did publication of more papers, books, documents, etc.

Early toxicologists were eager to share information and discuss their research.

A recent study (Lu and Wassom 1985) showed that the number of papers published in the field of toxicology (all disciplines) doubled during the decades of the 1970s and 1980s. As a result, the task of acquiring, using, and communicating toxicology information has become more difficult. Decades ago access to toxicology information was not a major problem because it could be obtained through the "invisible college" of communication with colleagues, attendance at scientific meetings, and the reading of a few key journals. However, as the art of toxicology became more sophisticated and research more important, investigators found their ability to acquire

The number of papers published in the field of toxicology doubled during the decades of the 1970s and 1980s.

information and keep up with new developments diminished significantly.

Toxicology Information Systems

About 20 years ago two separate President's Science Advisory Committees reviewed, in depth, issues concerning technical information. One of these reports was issued under the auspices of the President's Commission on Science and Information (1963), headed by Alvin C. Weinberg, who at that time was also Director of the Oak Ridge National Laboratory (ORNL). This report, entitled "Science, Government, and Information," stated "the technical community must recognize that handling technical information is a worthy and integral part of science." This report, above all others, was the first to call for the producers of information (scientists/researchers) to be actively involved in the management (access/use) of information. A later report (President's Commission on Science and Technical Information 1966), entitled "Handling of Toxicological Information," defined toxicology information as "all information descriptive of the effects of chemicals on living organisms or their component subsystems" and further indicated the necessity of "a computer-based comprehensive and exhaustive system for storage and retrieval of valid information on the interaction between chemicals and biological systems." The recommendations set forth in these two reports have clearly influenced the direction of most information systems development over the past two decades. Also, during this time, the availability and application of computer technology in information processing and management have evolved to the point that use of computers for data/information management has become routine. In 1970, for instance, there were only around 70 computer-readable databases, with an estimated fewer than 10 million records available; by 1981 this number had increased to 750 databases with over 250 million records, and on-line searches of these databases (information files) in the United States and Canada reached 6 million.

The technical community must recognize that handling technical information is a worthy and integral part of science.

The phenomenal growth in the creation of databases/information files has also carried over into the development of peripheral software systems for more efficient access and management of the information contained in these files or databases. Overall, this rapid growth of hardware and software has been focused for the most part on making the information retrieval process faster, more flexible, comprehensive, and cost effective.

The basic concept that should form the foundation of any toxicology information system, whether it is a database, file, computer network, or some other type, is that the system should be designed, developed, and maintained for the end user. Unfortunately, far too many of the toxicology information systems in operation have either forgotten this root concept or never gave it serious consideration in the first place. Proof of this can be easily obtained through conversations with active or practicing researchers in any of the toxicology disciplines. A majority, if questioned, will respond that

The recommendations of the 1966 President's Commission on Scientific and Technical Information clearly influenced the direction of most information systems development over the past two decades.

they do not use a particular database, file, or computer system because the specific type of information needed cannot be easily obtained. Unless the system is user-friendly and information formatted so that a query can be initiated using scientific terminology of the day, direct use by researchers will not occur. In my opinion, systems structured without these characteristics are destined to obtain a user frequency among practicing toxicologists of only 10 to 15%. This leaves an estimated 85 to 90% would-be users to obtain information via the "invisible college."

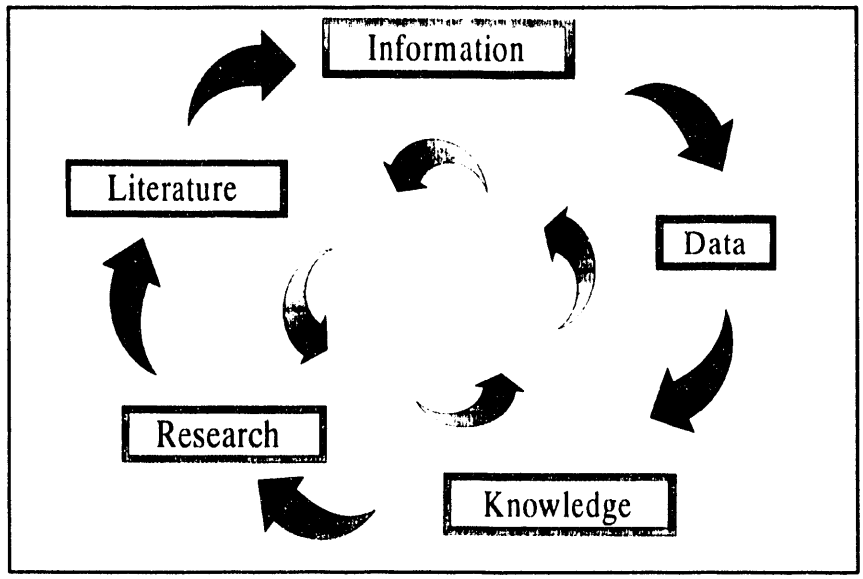

Fig. 1. The Information Cycle.

The production of information in the toxicological sciences follows the same pathway evident for almost any other area that strives to produce and use knowledge. This information pathway, illustrated in Fig. 1, is very simple and perhaps therein lies the problem. It is so simple that, unfortunately, a number of those responsible for development or maintenance of information systems forgot it or assumed wrongly that it is an intrinsic part of the system. As evident in the title of this symposium, "Access and Use of Information Resources in Assessing Health Risks From Chemical Exposure," the keyword is "information." Unless information systems designed to provide access to toxicological knowledge pay attention to the needs of the end user, they are worthless.

The Specialized Information Center Concept

Most of us know that the risk assessment process is composed of four steps: (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization.

To carry out or implement the conditions of these four steps, good reliable data/information must be available. Consider this issue: do you, as someone who has responsibility in risk assessment, have access to reliable and complete data/information? We would wager that if a survey were taken, 85 to 90% of you would say "No." In the military, information is equated with intelligence and, militarily speaking, we have not properly handled our intelligence. Most of the wisdom from the Presidential Commission on Science and Information in 1963 and 1966 remained locked between the covers of these two reports. The most significant pearls of wisdom from these reports is the idea for the specialized information center and the plea that those involved in the technical aspect of a science should become involved with the collection and use of the information

Those involved in the technical aspect of a science should become involved with the collection and use of the information generated by that science.

generated by that science. We are proud to say that these axioms have been followed with the origination, development, and maintenance of the toxicology databases/information files here at ORNL. Because of limitations in time and because most ORNL databases/information files have been elegantly presented in the poster sessions, this paper will focus on only one of these, the Environmental Mutagen Information Center (EMIC), to illustrate how the specialized information center concept was implemented at ORNL.

The Environmental Mutagen Information Center (EMIC)

In the late 1960s, the need for information accessibility in the area of mutation research was recognized by the newly formed Environmental Mutagen Society (EMS), which initiated action to provide access to the literature on mutagenicity and related subjects. As a result of the action taken by the EMS, EMIC was officially organized at ORNL in the fall of 1969, following the concept of the specialized information center as proposed in the Weinberg report. EMICs reason for being is to establish a means by which researchers and others could have ready access to the literature of genetic toxicology. A staff of dedicated people was assembled along with all possible methods and equipment to carry out this mandate. Prior to 1969, the genetic toxicology literature was in a state of disarray, and publication frequency was increasing each year (Table 1).

Records reveal that documents currently collected and indexed at EMIC were published in over 3800 different sources. This fact more than any other illustrates the futility of individual efforts

Table 1. Yearly publication frequencies for genetic toxicology literature

Year of publication	Number of documents
1967 and prior years	2527
1968	982
1969	1410
1970	1949
1971	2421
1972	2611
1973	2787
1974	2396
1975	2713
1976	2903
1977	3232
1978	3866
1979	3895
1980	4146
1981	4467
1982	4981
1983	4603
1984	4004
1985	3857
1986	3523
1987	3030
1988	2992
1989	3046
1990[a]	>4000
1991	3508
1992[a]	4000
1993[a]	4000

[a]Literature collections for these years are incomplete; numbers shown are projections.

EMIC's reason for being is to establish a means by which researchers and others could have ready access to the literature of genetic toxicology.

to access the genetic toxicology literature. Interestingly enough, as of May 1991 almost half of the over 78,000 EMIC papers surveyed were published in about 30 key journals (Table 2). For this reason, it is recommended that libraries located at institutions actively engaged in genetic toxicology research provide easy access to these key journals, particularly *Mutation Research*, *Environmental and Molecular Mutagenesis*, and *Mutagenesis*.

Publications selected to become a part of the EMIC information file are indexed by a group of skilled staff members. EMIC's document selection and indexing procedures are thoroughly explained in Wassom (1973, 1980) and Wassom and Malling (1978). These procedures are briefly reviewed here to explain how the EMIC file is constructed and how it may be used to access the genetic toxicology literature.

After a document is selected for entry into the EMIC file, a copy is obtained and index terms describing the bibliographic data, agent/organism, keywords, and Chemical Abstracts Service (CAS) Registry Numbers are recorded and entered in the computer. Table 3 shows an example of this type of entry.

The next step in the indexing scheme focuses on the indexing of information pertinent to assay systems and/or genotoxic endpoints. Only papers containing original experimental data are indexed: indexing terms note the assay system used or genotoxic endpoint that is either looked for or observed. Exceptions to this policy include reviews, symposia, book chapters, and abstracts considered pertinent by an EMIC staff member. All papers to be indexed with these parameters are first judged on content and are grouped into one or more of the eight general categories shown in Table 4. On completion of this general grouping, the more specific index terms are then assigned where appropriate (e.g.,

Table 2. Key journal sources used by the Environmental Mutagen Information Center

Biochemical Pharmacology
Biochimica et Biophysia Acta
Biochemistry and Biophysics
Canadian Journal of Genetics and Cytology
Cancer Letters
Cancer Researc'i
Carcinogenesis
Cell Biology and Toxicology
Chemico-Biological Interactions
Cytology and Genetics (USSR)
Environmental and Molecular Mutagenesis
Environmental Health Perspectives
Experientia
Experimental Cell Research
Federation Proceedings
Genetics
Hereditas
Human Genetics
Japanese Journal of Genetics
Journal of Bacteriology
Journal of the National Cancer Institute
Molecular and General Genetics
Mutagenesis
Mutagenesis, Carcinogenesis and Teratogenesis
Mutation Research
Proceedings of the American Association of Cancer Research
Proceedings of the National Academy of Sciences USA
Radiation Research
Science
Soviet Genetics (USSR)
Toxicology
Toxicology and Applied Pharmacology
Toxicology Letters

GM, HGPRT assay or EC, chromosome aberrations).

The information indexed by EMIC can be accessed via computer in a variety of ways: compound, organism, assay system, or end point. The fields indexed can be queried individually or in combination with information in other fields. This capability provides a powerful tool for the researcher, particularly in document selection and subject evaluation. Because it is not possible to provide illustrations for the many genetic toxicology assay systems, users may contact EMIC directly for further information on particular systems of interest. The EMIC file can be accessed directly via the National Library of Medicine TOXLINE/TOXNET* computer systems.

Conclusion

The illustration using EMIC as an example of the specialized information center concept clearly shows how a file can be developed for use by a specific toxicology discipline in concert with researchers of that discipline. The process is not easy but with perseverance it can be done.

Kathy Deck of the Agency for Toxic Substances and Disease Registry** put together a listing of some of the available sources of computerized information on toxicology and environmental health. These listings, although not inclusive of all the various files, databases, books, etc., available for these subject areas, are

Table 3. Example of the scheme used by EMIC during its first phase of document indexing

Accession number	077618
Authors	Warr, Tracey J.;Parry, J.M.; Callander, R.D.; Ashby, J.
Title	Methyl vinyl sulfone: A new class of Michael-type genotoxin
Publication source	*Mutation Research* 245:191-199
Publication date	1990
Literature type	Journal article with original data
Test object, common classification	Bacteria; Mammal, Chinese hamster cell culture
Test object, specific classification	SALMONELLA TYPHIMURIUM,TA98, SALMONELLA TYPHIMURIUM,TA100, SALMONELLA TYPHIMURIUM,TA1535, SALMONELLA TYPHIMURIUM,TA1537, SALMONELLA TYPHIMURIUM,TA1538; CRICETULUS GRISEUS
Tissue culture	Don-WG3H Cells; LUC2 Lung cells
Agents and Chemical Abstracts Service Registry Number (CASRN)	Methyl vinyl sulfone (3680-02-2); Acrylamide (79-06-1); Microsomes,rat,S9 (NO CASRN)

Table 4. Major EMIC categories used for the classification of assay systems and/or biological end points

Effects on nucleic acids (EN)
Gene mutations (GM)
Effects on chromosomes (EC)
Cytological effects (CE)
Mitotic or meiotic effects (MM)
Plant pigment mutation (PM)
Fertility and sterility studies (FS)
Miscellaneous studies and/or effects (MS)

*For further information about Toxline or Toxnet, interested individuals may contact Specialized Information Services, National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894.

**For further details about the listing of sources for computerized information on toxicology and environmental health, please contact Kathryn S. Deck, Information Resources Management Group, Center for Environmental Health and Injury Control, Chamblee 27 F-29, Centers for Disease Control, Atlanta, GA 30333.

valuable compendiums that show the vast nature and divergent types of systems and books available to the toxicology information consumer. Which of these offer the best means of accessing the literature? You, as users, should study each of them well, keeping in mind the admonitions expressed by the Presidential Commission on Science and Information of 1963 and 1966. Make your selections wisely so that you can have confidence that your future decisions, research, or risk assessments have been based on the best information/data available. In closing, we ask that as representatives of both state and federal agencies you remember these points:

- You must accept or share with others the responsibility for information activities connected with the various scientific and technical areas associated with fulfillment of your mission.
- Short-comings, deficiencies, etc., that are noticed in information activities should be voiced and demands for improvement made through and with the support of the appropriate scientific and/or technical society.
- Federal and state agencies must devote an appreciable portion of their talents and funds to support information activities.
- Information should become a highly placed focal point for all government agencies.
- Information activities should be maintained in the research and development environment of an agency, laboratory, etc., and not as an administrative function.

If these guidelines are followed, the information activities for the toxicology sciences can and will evolve to a more usable state rather than become extinct through nonuse.

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Information and Technology: A Coexistence Without Limits, A Beginning With No Apparent Ending

David J. Reisman, U.S. Environmental Protection Agency

A variety of issues must be addressed in development of software for information resources. One is accessibility and use of information. Another is that to properly design, abstract, index, and do quality control on a database requires the effort of well-trained and knowledgeable personnel as well as substantial financial resources. Transferring data to other locations has inherent difficulties, including those related to incompatibility. The main issue in developing health risk assessment databases is the needs of the user.

To those of you who have come not knowing what to expect at this symposium, one good description might be that this is the first attempt to really view the ways in which information and technology are used to advance the health risk assessment process. This morning, the information needs of the risk assessors and the risk managers were reviewed.

I am a database manager and have worked in the health and environmental risk area within the Environmental Protection Agency (EPA) in Cincinnati for 12 years. I have written and reviewed many different types of health assessment documentation and methodology, including ambient and drinking water criteria documents, health advisories, and environmental health documents, plus the various EPA health risk assessment methodologies. I have experience as a risk assessor, but not a risk manager. Through all of these work experiences, I have observed that technology has been providing information at a faster pace in recent years. Yet, with each step in growth, demand for more data "at your fingertips" creates the need for more advanced technology. The coexistence will always improve, but the indefinite limits of this growth depend on many other variables. The automated databases created over the last 30 years are still only the beginning. A glimpse at artificial intelligence and its possibilities illustrates how much immediate, as well as long-term, growth can occur.

Automated databases created over the last 30 years are only the beginning.

In preparation for this talk, I began to retrace the steps that brought me to information science. When I was just starting college, I frequently went between our computer science department and our computer room, which was a quarter mile walk. I always carried boxes of computer cards because that's how we did databases in "those" days. The programming watchword was "always number your computer cards." One day I stumbled down a few steps, only to catch my balance but not my now-mixed cards. Today, we don't carry cards, and we don't

The programming watchword was "always number your computer cards."

walk; we telecommunicate! Technology has had a tremendous impact on information flow. Although beneficial in many ways, this impact has affected health risk assessment scientists because they can be overwhelmed by the sheer quantity of information. Even with the information and data, without appropriate science and methodology, it is still a challenge for risk managers and decision-makers to provide the best risk-based decision. Risk assessors often provide the research data with their best analysis, along with those data provided by other interested groups; but then the risk manager is "caught in the middle" of all these different parties and their respective scientific analyses and conclusions with, in most cases, no previous experience upon which to base a decision. Generally, it is still better to have conflicting data than to have none at all. The capability to provide that information quickly has made risk analysis much more meaningful, and hopefully, more scientifically valid than it was previously.

One of the purposes of this symposium is to look at accessibility and use of information resources in health risk assessment. The first slide states, "research yields information which provides better technology to conduct more research." This little statement defines a large aspect of risk assessment research. It is a continual process, almost like a loop or a real Catch 22. More research yields more information, and along with additional information are advances in technology that allow us to conduct better research, which again comes back to providing more information. Statisticians sometimes say that one can never have enough data, because more data can make assessments both precise and accurate. In this process, technology appears to be a promoter of the whole information process, and as technology is improved there is a seemingly endless promotion of the process. The following is a discussion of parts of the information process and its technology, along with some of the problems and pitfalls inherent in it.

It is a continual process, almost like a loop or a real Catch 22.

To properly design, abstract, index, and do quality control on a database requires the effort of well-trained and knowledgeable personnel, as well as substantial financial resources. Most databases in the health risk assessment area are being developed by the government. Obviously, because of the substantial financial requirement, private industry would have to be assured of return on that investment before becoming involved. Thus, the transfer of information is highly dependent on the transfer of dollars, either for purchasing of equipment or developing information tools.

To properly design, abstract, index, and do quality control on a database requires the effort of well-trained and knowledgeable personnel.

In planning an information tool the creators sometimes have an idea of what they want, and know what technological tools are available to them, but do not have a total view of who or why people would use products outside their limited immediate arena. In an attempt to go beyond this immediate arena, the EPA's Chemical Unit Record Estimates (CURE) database was planned over nine months. Much of this time was used to analyze available data and the different types of documentation that the EPA

Office of Heath and Environmental Assessment (OHEA) produces. From this review, the needed data fields were determined, and then the actual building of the database was begun. However, many times an information tool is an outgrowth of a smaller "pilot" project. Then, another group slightly alters the original to fit a new or expanded need, or older databases are made more useful because of better computer software and hardware. But in the development stage, it seems that efforts constantly have to be repeated. Again, the circular motion is created because as data are abstracted, indexed, and then reviewed, the need to change certain fields becomes obvious. In most databases, the ever-evolving process of updating and upgrading never stops. One thing to try to avoid in building databases, is the dilemmas. With luck, the dilemmas won't become the last stage, disaster, which usually marks the end of the database. This phase follows funding cuts and loss of involved personnel.

Even with a great database staff, things are sometimes overlooked. For example, once the prototype is built and sent to many of your user groups, the telephone rings and you get a person on the other line who says, "Why doesn't this work?" One common experience is the problem of the novice user. Sometimes the problem is simply that the user has a low density drive on his computer and has been sent a high density disk. Often a simple problem can be overlooked because the users come in all experience categories.

Transferring data to other locations always creates dilemmas. For example, I once sent a program to somebody in a Washington, D.C. office for review. The person at the other end called me, and after almost an hour and a half, we still couldn't understand why the program wasn't working. I sent a batch of new diskettes, and the same thing happened again. After about two days, I found that while I was using color monitors, this person was still using a black and white. When the program translated down to the black and white monitor, the highlight bar could not be seen because it was staying in the background. This also happened when running some of our programs on the laptops with plasma displays. These are some of the unexpected technology pitfalls. Technological advances can also mean that you must reverse or retrace your previous efforts to insure accuracy and precision.

Some older databases can now be made more useful.

The main issue we must examine in developing health risk assessment databases is the needs of the user. Technology has changed and developed, allowing us to store large amounts of data on smaller, portable machines. The risk assessor can now carry a machine to a site and have quite a bit of relevant data at hand, but the question remains, "Does he have the ability and training to make these decisions immediately?" If several computer systems contain large amounts of data, the end user could purchase an expensive laptop that has a large hard disk, but would all this information help or would it make the job even more difficult? Information personnel in the health risk

Transferring data to other locations always creates dilemmas.

assessment field have the ability to develop worthwhile and sensible tools. However, they must make sure that these tools are of good quality, not just great quantity, and must be useful and available. If cost is the limiting factor, then resources should be used wisely.

The development of different databases on different software creates another technological difficulty: incompatibility. This term can cover a wide variety of areas. For example, on one side of PC-development are the "Independent Banana Merchants", and on the other side we have the "Apple sellers"; two commonly used company machines that can't talk well to each other. What good are databases if they are limited only to a certain type of user or certain type of machine? It may seem to the non-computerized risk assessor that a lot of information is available and can be transferred at will, but the transfer process is not easy, takes too much valuable time, and therefore frequently is not worth the effort. Incompatibility also is not just in the equipment or the software. There is also the incompatibility of database managers who do not talk to each other because of the "my turf" attitude.

New software is constantly appearing on the market, or current versions are changed or updated so that even persons using the "same" software may not be compatible. A prime example is the little message "Incorrect DOS version" which is displayed when work done on one machine is transferred to a machine with a lower version of DOS which consequently won't run. An inexperienced user may keep trying to no avail, but although the program will not run, it is not damaged. The user then calls the person in his office that he/she needs the most: the resident "chiphead" who understands hardware and software. It reminds me of the salesman who sold me my first PC after I had only a few weeks of PC experience. I didn't know what he was talking about, so I just said, "Well, I don't understand, so I'll take that one. It looks nice, has good features, and it's got a nice color monitor."

The main issue that we must examine is the needs of the user.

Previously, people carried calculators; now they carry laptops or computerized workbooks to meetings. The real question now is, can we manage all of this? As a person who works in both the information science area and with health effects documentation, I think it's very difficult. We have a big job ahead of us, but we shouldn't get dismayed because today we have better information than ever to do our assessments.

In connection with this is one of my other chief points — proliferation. When I was in graduate school, some of our experiments were on planarian regeneration. You cut away a piece of the planaria and it regenerates that piece. You do the same thing to a hard disk on a PC. You remove 3 MB of data so that you will have room for another program, but, 2 weeks later you are back where you started. It seems that information on a hard disk constantly regenerates or replaces itself. Two years ago, I got a 300 MB hard disk as a solution. Today I need a 600 MB hard disk! At this point, what we really have to

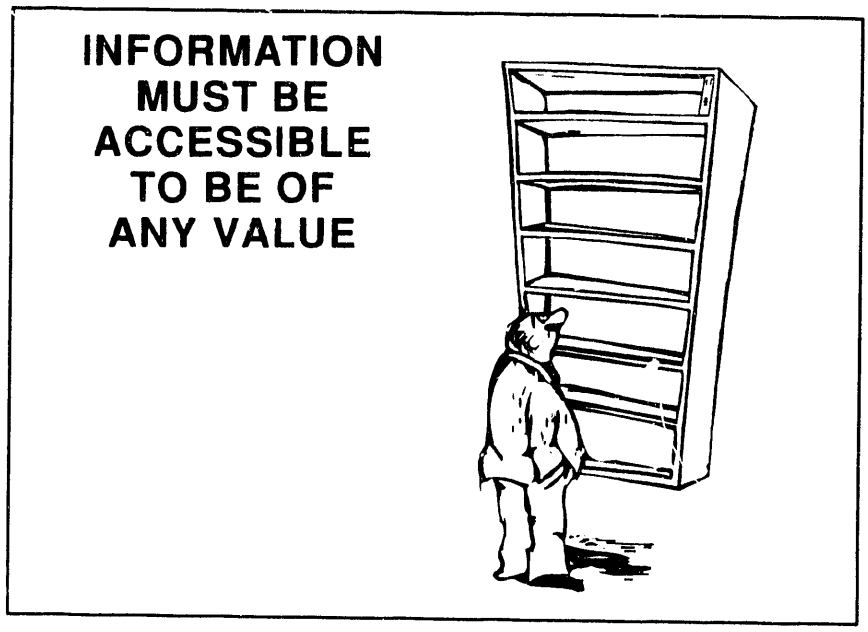
The transfer process is not easy, takes too much valuable time, and therefore frequently is not done.

look at is the possibility of information overloading brought on by expanding technology. Every office needs a good information manager.

Risk assessors must inform the information personnel and the researchers exactly what type of data is needed in order for a true "applied" research project to be conducted. By achieving this level of communication, we will be able to get the proper type of information and data on which to base our risk management decisions. The technological tools are available, but the current communication among various associated risk assessment sectors is still in its infancy.

My final point is that of accessibility represented by this figure of a gentleman standing in front of a bookshelf that is over 10 feet high. Naturally, the book that he wants to read is on the top shelf with no ladder in sight. Information must be accessible to be of any value.

We have the information and the technology is available; friendly and usable systems must be developed to make the data accessible to all who need it.



Can we manage all of this?

The Challenge of Information Access

Linda A. Travers, U.S. Environmental Protection Agency

Traditional methods of risk communication may not work for large quantities of information. Federal databases are being created to meet the public's right-to-know.

The "public right-to-know" about the business of government is a fundamental principle of our democratic government and open society. As the public becomes more interested in environmental issues, they expect to receive information and get answers from federal and state officials. A local citizens' action group may want to gather information to gain support for or against local landfills or municipal waste incinerators. Traditional methods of risk communication may not work for such large quantities of information; as a consequence, federal databases are being created to meet the public's right-to-know.

Over the past two decades, the federal government has systematically exploited computer and communications technology to conduct its business more effectively, efficiently, and economically. The government has learned it must also answer the public's questions.

In the process, federal agencies have converted public information from paper documents and data files into electronic database systems. Federal agencies routinely manipulate this computer data to fulfill agency missions ranging from determining the risk of a potentially hazardous substance to ascertaining where the next enforcement inspection should be conducted. A growing number of agencies require businesses to provide data collected for regulatory purposes in electronic formats and in turn the government fulfills its information disclosure responsibilities by disseminating public information through government, commercial, and nonprofit interactive computer and communications networks.

This fundamental transformation of public information and public decision making into computerized data processes occurred without serious public policy attention being paid to how it may affect the public's right-to-know. Moreover, little public policy debate or concerted effort has been initiated to resolve electronic information policy issues, citizen access rights being a core concern.

I suggest that the debate has begun. You can expect to hear more about the government's responsibility and obligation to share information with the public. Public action groups are beginning to form with the very specific purpose of seeking out and analyzing information that the government collects from industry.

Federal databases are being created to meet the public's right-to-know.

This fundamental transformation of public information and public decision- making into computerized data processes occurred without serious public policy attention being paid to how it may affect the public's right-to-know.

Senator Jeff Bingaman (D-NM) has written the Federal Information Resources Management Act of 1989 (S. 1772) to reauthorize the Paperwork Reduction Act. The legislation was introduced in a series of hearings in 1989 in the Subcommittee on Government Information and Regulation. Subsequent hearings on the bill by the full Committee on Government Affairs were held in February 1990. S. 1772 promotes availability and public access to information in several ways, including:

"Agencies, not Office of Management and Budget (OMB), have the primary responsibility for decisions about dissemination activities, and those agencies are required for the first time to establish a sound information dissemination management program." According to this bill, public access must be equitable and equal.

Another example of this new public access debate can be found in the House of Representatives bill to create the Department of Environmental Protection (H.R. 3847). Unlike the Senate version, this bill's public access provisions are far reaching. This bill would require the newly created department to write a guide to environmental information services, products, and systems; develop methods for cross-linking and integrating environmental data; create a study, incorporating pilot projects, to show ways to use computers to disseminate information; and set up an advisory committee to recommend improvements in public access. No new appropriation of funds is linked to this proposed responsibility.

The real-time example this paper will discuss is the Environmental Protection Agency's (EPA) large precedent-setting sharing of environmental data. We have responsibility for designing and implementing an environmental database—the Toxic Release Inventory (TRI), which Congress directed the EPA to create specifically to be shared with the public. We began collecting data from industries in 1988 and now have 2 years of experience with the system and the public's use of the database. Today, information on the estimated annual releases of 320 chemicals or mixtures from over 20,000 emitters resides on a user-friendly computer at the National Library of Medicine for all the world to use.

We have responsibility for designing and implementing an environmental database—the Toxic Release Inventory (TRI).

During the first year of operation, nearly 170,000 searches of the database were made.

These searches were not just done out of curiosity. The information is being used in a variety of ways. Companies are comparing their performances to those of their competitors and deciding to make dramatic voluntary reductions in their toxic releases. Citizens are studying the releases in their communities and demanding information to assist them in their public policy debates. The release of this information creates a strong demand for more information to be collected and consolidated by EPA and state environmental agencies.

The information is being used in a variety of ways.

Not everyone feels comfortable using computers, so the EPA is also providing information from the TRI in many traditional nonelectronic ways. These include a National Report, which is an easy to understand sum-

mary of the database. The database is also on microfiche at over 3300 county libraries in the country. Diskettes of each state's emission reports have been distributed to each State Health or Environmental Department, and more than 500 Depository Libraries have the database on CD-ROM. All of these products are for sale to the general public from either the Government Printing Office or the National Technical Information Service.

I hope that talking about our experience at EPA with TRI helps convince you that the debate on the principle of Right-To-Know and Public Access to government information is of critical importance today. I think this point is best summed up by a quote of Senator Bingaman. He said: *Our nation's information strategy must also include an affirmative responsibility for public access to government information. Unfortunately, our laws governing information policy have not yet enabled our society to benefit fully from the advantages offered by the "information age."*

By now you must be saying to yourself, "What does this have to do with me and the information I manage or use?" The new 1990s challenge to environmental scientists and managers will be public access to information, information which in the past we have kept for our exclusive use to support activities such as research and development or government rule making.

With that challenge facing us, a number of actions can be taken to enhance our ability to accept that challenge and improve our use of environmental data in government decision making. It is important that risk communication mechanisms evolve at the same pace as the improvements to our environmental data. We must continue to foster outreach efforts so that our data is accurately communicated in an understandable manner and is made available to all citizens.

Actions can be taken to enhance our ability to accept the challenge and improve the use of environmental data in government decision-making.

Many "how to" guidance documents are available to help you develop traditional informational brochures and other materials for the public's use. I encourage all of you to work with your staff and with risk communication specialists to create easy to understand public information.

As we move towards computer access, we are faced with unique challenges. The following are three major information management principles that we set for ourselves in creating the TRI database that can help meet access goals now and in the future.

- Standardization of Data Fields;
- Integration of Data Bases, where appropriate; and
- Data Quality/Data Control Processes.

Based on the experience we gained from making TRI publicly available, these three principles are the most important issues for government information managers to focus on in the next few years.

There are three major information management principles that we set for ourselves in creating TRI.

Government managers and database developers should be sensitive to the need to standardize data fields across databases. Two such fields that lend themselves to such an approach are location data and facility identification data. Both of these data fields are important when doing any sort of

trends or geographic exposure analysis. Efforts should be made by database developers to standardize as many of these types of data fields as possible. Such an effort will help increase the ability of users to integrate information across databases, which is the second principle to highlight.

As we move into cross-media risk and exposure assessments, the ability to integrate information across databases becomes more important. Database developers should think about how their data will be used by others in the government as well as outside the government. We must move away from databases that are for the exclusive use of a few people and move toward databases that will be searched by a broad spectrum of users.

I work at EPA, so I know it is no simple matter to start thinking and working with our information in this very different way. We have very tight budgets for information purposes. This may indeed be called the "information age," but you couldn't tell it from the way we are forced to budget. Information is still seen as a frill—a convenience, not a necessity. However, this attitude is changing, and in the competition for resources nothing sells a budget better than to tell those in charge of resources that you have a highly vocal set of users who are clamoring for enhancements. Strong indications that the data are wanted and are being used to protect the environment (for example) should help kill the myth that information is merely a frill that can be budgeted for only in good years, and cut back in lean years. Integration of data across data bases can help reinforce the argument for appropriate resources.

States are also coming into the "Information Age." Many more opportunities exist to share information and enter into partnerships between the federal and state levels of governments.

The final point is the need for a good quality assurance and quality control (QA/QC) process for your data collection. This is the most important lesson learned in collecting the TRI data. The original policy decision, because of resource constraints, was to enter the data collected exactly as provided by the submitter. As you can imagine, this caused many problems with the quality of the database and reliability of the information that users retrieved. Now, EPA is fully applying appropriate QA/QC process to the TRI database.

TRI is evolving as users find new ways to analyze the data and as we learn how to make this public right-to-know experiment work better. Congress directed us to build this system for the people, and we are still learning the best techniques to make TRI work for everyone.

Move away from databases that are for the exclusive use of a few people and move toward databases that will be searched by a broad spectrum of users.

TRI is evolving as users find new ways to analyze the data and as we learn how to make this public right-to-know experiment work better.

Structure Activity Relationships to Assess New Chemicals Under TSCA

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Under Section 5 of the Toxic Substances Control Act (TSCA), manufacturers must notify the U.S. Environmental Protection Agency (EPA) 90 days before manufacturing, processing, or importing a new chemical substance. This is referred to as a premanufacture notice (PMN). The PMN must contain certain information including chemical identity, production volume, proposed uses, estimates of exposure and release, and any health or environmental test data that are available to the submitter. Because there is no explicit statutory authority that requires testing of new chemicals prior to their entry into the market, most PMNs are submitted with little or no data. As a result, EPA has developed special techniques for hazard assessment of PMN chemicals. These include (1) evaluation of available data on the chemical itself, (2) evaluation of data on analogues of the PMN, or evaluation of data on metabolites or analogues of metabolites of the PMN, (3) use of quantitative structure activity relationships (QSARs), and (4) knowledge and judgement of scientific assessors in the interpretation and integration of the information developed in the course of the assessment. This approach to evaluating potential hazards of new chemicals is used to identify those that are most in need of additional review or further testing. It should not be viewed as a replacement for testing.

Introduction

TSCA was enacted and signed into law by President Gerald Ford on October 11, 1976. It went into effect on January 1, 1977. Simply stated, TSCA provides EPA with the authority "to regulate commerce and protect human health and the environment by requiring testing and necessary use restrictions on certain chemical substances . . ."

TSCA has two main regulatory features: (1) acquisition of sufficient information by EPA to identify and evaluate potential hazards from chemical substances and (2) regulation of the production, use, distribution, and disposal of such substances where necessary. Although TSCA consists of 31 sections, principal provisions of the act are described in Sects. 4 (Testing of Existing Chemical Substances), 5 (Premanufacturing Notices for New Chemicals), 6 (Regulation of Hazardous Chemical Substances), 7 (Imminent Hazards), and 8 (Reporting and Retention of Information).

This paper will deal with the use of quantitative structure activity relationships (QSAR) to assess new chemicals submitted under Sect. 5. Particular reference will be made to the use of mutagenicity data in this context.

Quantitative structure activity relationships (QSAR) are used to assess new chemicals submitted under Section 5 of TSCA.

Premanufacture Notice

Under Sect. 5 of TSCA, a manufacturer must notify EPA 90 days before manufacturing, processing, or importing a new chemical substance. A "chemical" may be any of a wide variety of organic or inorganic substances manufactured or imported by the chemical industry for uses such as dyes, pigments, lubricant additives, chemical intermediates, synthetic fibers, structural polymers, or coatings. Essentially, it includes any commercial chemical except those used as drugs, pesticides, food additives, cos-

metics, and certain other uses that are controlled by other statutes.

"New" is defined as any chemical not listed on the Inventory of Existing Commercial Chemicals. The inventory was first compiled in 1977 and included those chemicals that were being manufactured or imported for use at that time. Since then, PMN chemicals for which EPA has received a Notice of Commencement (NOC) have been added to the inventory, which now includes over 60,000 entries. Since 1979, EPA has received over 7000 PMNs. Of these, approximately 60% were discrete chemicals and approximately 40% were polymers. TSCA requires that certain information be provided in the new chemical notification. This includes chemical identity, production volume, proposed uses, estimates of exposure and release, and any health or environmental test data that are available to the submitter at the time of submission.

Section 5 contains no explicit statutory authority requiring manufacturers, processors, or importers to conduct testing of new chemicals prior to their entry into the market. Therefore, approximately 50% of all PMNs received contain little or no test data. The types of data received and the distribution of this data between nonpolymer and polymer chemicals are shown in Table 1. Although the data shown in the table are for the years from 1979 - 1985, figures should be regarded as substantially accurate because the rate of

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Table 1. Percentage of data by type submitted with premanufacture notices, 1979 - 1985

Type of data	All (%)	Nonpolymers (%)	Polymers (%)
None	51	38	68
Toxicity	40	53	24
Acute toxicity			
Oral	40	53	24
Dermal	23	29	14
Inhalation	11	13	7
Skin/eye irritation	38	48	21
Sensitization	11	17	5
Mutagenicity	15	23	6
Other	11	16	4
Ecotoxicology	10	15	4
Environmental fate	9	13	4

data submission with PMNs has not changed appreciably in the period from 1985 - 1990. Note that data received are associated primarily with nonpolymer submissions. Most of the data received are acute oral toxicity data. Mutagenicity data, primarily the results of testing in the Salmonella/mammalian microsomal assay, are received with 5% of all PMNs.

Because of the paucity of data associated with PMN submissions, the assessment of potential toxicity of new chemicals is conducted using special techniques developed for this purpose. These include (1) evaluation of available data on the chemical itself, (2) evaluation of data on analogues of the PMN chemical, on its metabolites or their analogues, (3) use of QSARs, and (4) knowledge and judgement of scientific assessors in the interpretation and integration of the information developed in the course of the assessment. The use of QSARs is limited to the estimation of (1) physical chemical properties such as water solubility, log P, and vapor pressure, and (2) acute aquatic toxicity and bioconcentration factors, which can be estimated on the basis of log P. Currently, EPA does not use QSARs for health effects because too few endpoints and too few classes of chemicals have been studied to permit routine use of such methodology in PMN assessments.

Evaluation of PMN Chemicals

In evaluating chemicals under Sect. 5, EPA must distinguish between those that may present a "reasonable" risk to health or the environment and those that present an "unreasonable" risk. Risk is defined as a function of hazard, which includes a determination of both toxicity and exposure; unreasonable risk also includes a consideration of exposure. EPA has 90 days from the receipt of submission of a PMN to make this determination. The schedule for the assessment process is shown in Table 2.

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During the first week after a PMN is received, it is presented before a Structure Activity Team (SAT) composed of chemists, toxicologists and environmental scientists. Using professional judgment based on knowledge of relevant structural analogues, the SAT expresses concern for potential environmental effects or for health effects, which may include cancer, mutagenicity, teratogenicity, neurotoxicity, or other chronic or acute effects. Concern is not expressed for all chemicals. Likewise, when concern is expressed for a particular PMN chemical, it is not necessarily expressed for all effects. Within 1 week of the SAT meeting, a second meeting is held at which the SAT concerns, the use scenario, and expected exposure are considered together and a decision is made on whether or not to continue the review process (Detailed Review).

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Once a chemical enters into the Detailed Review Process, a team of health and/or environmental experts is convened. Each expert examines the PMN from the perspective of his or her area of expertise and makes a case using direct or supportive evidence. Direct evidence includes data dealing specifically with the PMN chemical. Such data may

Table 2. Premanufacture notice (PMN) hazard assessment process

Day	Activity
0	Receipt of notice
2–9	Determine chemical nature Review submitted test data Identify suitable analogues including analogous PMN chemicals Perform preliminary literature searches on the PMN chemical and relevant analogues Obtain in-house data on analogues, if available
10	Chemistry team meets
11	Structure activity team (SAT) meets to discuss fate and health and ecotoxicology hazards
14	Exposure analysis team meets to discuss occupational, consumer and environmental exposure
15	Preliminary risk decision is made Low risk cases are dropped from further review. Others enter into a detailed review for analysis of risks
16–60	Detailed review Analogue identification continues, literature searches are performed, and relevant literature is identified and acquired Available data, including any available on the PMN chemical, are reviewed and evaluated The PMN is evaluated to determine such factors as absorption, metabolism, and the potential for activation/deactivation in the body A written hazard assessment is prepared utilizing the data developed and relating the data on the analogue to the PMN chemical
65	Internal peer review of hazard/risk conclusions and development of testing recommendations
80	Final risk decision Cases that do not appear to present an "Unreasonable risk of Injury" are dropped Chemicals that "may present an unreasonable risk" are subject to regulatory action (e.g., exposure controls may be specified, restrictions may be placed on use, or testing requirements may be specified)

have been submitted with the PMN or may have been found in the scientific literature.

Supportive evidence may include data on a potential metabolite of the PMN or data on a close structural analogue of the PMN or on analogues of a potential metabolite. Because data on the PMN itself is generally not available, most evidence is supportive in nature. To be useful as supportive evidence, analogues selected must fulfill two requirements: (1) they must resemble the PMN or its potential metabolites structurally, functionally, in physiochemical properties, electronic potential, or some combination of these factors, and (2) they must offer the promise of a productive literature search.

After the completion of the detailed review, several courses of action may be taken by the agency.

1. The agency may determine that the chemical poses no unreasonable risk to health or the environment. In that case, manufacture of the chemical may begin following the expiration of the 90-day period. On receipt of an NOC from the submitter, the chemical is added to the inventory of existing chemicals and is no longer considered a "new" chemical.
2. If it is determined that there is enough information on which to base a judgement that a chemical presents an unreasonable risk, the agency may issue a proposed rule that will initiate some type of direct control of the chemical. If it is determined that a total ban is required, the agency may issue a proposed order to prohibit manufacture under Sect. 5(f) of TSCA.
3. If it is determined that there is insufficient information on which to base an evaluation of the chemical, that it may present an unreasonable risk of injury to health or the environment or may be manufactured in sufficient quantities to cause significant environmental or human exposures, the agency may issue a proposed order to prohibit or limit the production of the substance under Sect. 5(e) of TSCA. As a result of a Sect. 5(e) order, the company may be required to submit data following specific testing of the PMN or it may be required to control exposure levels by the use of protective clothing or equipment. Section 5(e) orders may also limit manufacture for designated uses only.

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Use of Mutagenicity Data

In general, mutagenicity data are used for three purposes under Sect. 5: (1) as part of exposure-based testing, (2) to assess the potential of the PMN chemical to induce heritable genetic effects, and (3) as part of the weight of evidence that a chemical may be a potential oncogen.

The criteria for exposure-based testing and the tests required when such triggers are met are shown in Tables 3 and 4. Not all tests are necessarily performed on all chemicals that satisfy the conditions for exposure-based testing. When mutagenicity testing is required, the agency asks for a two-test battery of the *Salmonella* assay and a mouse micronucleus assay. Because the intraperitoneal route is

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Table 3. TSCA Section 5 criteria for exposure-based testing

1.	> 1000 workers exposed
2.	> 100 workers exposed by inhalation to 10 mg/kg/day
3.	> 100 workers exposed by inhalation to 1 - 10 mg/kg/day for 100 days/year
4.	> 250 workers exposed by routine dermal contact for 100 days/year
5.	Presence of the chemical in any consumer product where the physical state of the chemical in the product and the manner of use would make exposures likely
6.	> 70 mg/year exposure via surface water
7.	> 70 mg/year exposure via air
8.	> 70 mg/year exposure via groundwater
9.	> 10,000 kg/year release to environmental media
10.	> 1000 kg/year release to surface water after calculated estimates of removal by treatment

Concern for a chemical's ability to induce heritable gene or chromosomal mutations is rarely supportable under Section 5.

Table 4. TSCA Section 5 testing requirements for high-volume chemicals

1.	Acute oral toxicity test in rats
2.	28-day repeated dose oral study in rats (may include developmental, reproductive, or neurotoxicity testing)
3.	*Salmonella* assay and *in vivo* micronucleus assay
4.	LC_{50} in *Daphnia*, LC_{50} in fish, and bioassay in algae

considered most sensitive by agency scientists, it is required for the micronucleus assay. At this stage of testing, the emphasis is on determining intrinsic mutagenic potential and not on a determination of risk. If risk were a prime consideration at this point, then routes of administration that are more relevant to human exposure might be chosen for testing.

Because of the nature of the PMN assessment process, which relies heavily on the use of analogue data, and because of limitations in the size of the data base of chemicals tested for heritable genetic effects, concern for a chemical's ability to induce heritable gene or chromosomal muta-

tions is rarely supportable under Sect. 5. In the few instances in which such a concern has been supported, required testing has included the dominant lethal assay and assays for chromosomal aberrations in testicular cells. It is understood when such testing is required, that if positive, additional tests (e.g., a heritable translocation assay) may be required for risk assessment purposes.

The principal use of mutagenicity data under Sect. 5 has been as part of the weight-of-evidence that a chemical may be oncogenic.

In supporting a concern for potential oncogenicity of a PMN chemical, the agency will generally cite data on an analogue that is known to be oncogenic (i.e., demonstrated tumor-forming ability in one or more animal studies). In such instances, mutagenicity data on the PMN chemical or on the analogues are used to lend support to the case for potential oncogenicity. In cases in which no analogue of the PMN chemical has been tested for oncogenicity, mutagenicity data alone are generally not considered sufficient to support a concern for potential oncogenicity. Regulatory action is seldom, if ever, taken on the basis of mutagenicity data alone, especially on the basis of in vitro mutagenicity data.

Mutagenicity data have been required as part of several Sect. 5(e) notices. Initially, these requirements were primarily for *Salmonella* test data. For certain classes of chemicals, the requirement was for in vitro gene mutation data, specifically, for data from the mouse lymphoma L5178Y TK $^{+/-}$ system. More recently, the agency has begun requiring certain manufacturers to submit data from a battery of tests that has included the *Salmonella* assay and an in vivo assay for chromosomal effects, especially the micronucleus assay.

Where an appropriate oncogenic analogue has been tested in the same assays as those required for the PMN chemical, this agent is generally included in the test as a positive control chemical. In some cases, where activity of the analogue chemical in short-term tests was not known, the agency has required the simultaneous testing of both the PMN chemical and the analogue. Positive results for both the PMN chemical and the analogue are used to support the weight-of-evidence that the PMN chemical may be an oncogen. In these instances, a 2-year bioassay of the PMN chemical or the use of protective equipment to limit exposure is generally required.

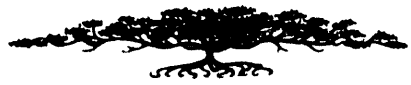
Negative results for the PMN chemical, in the face of positive results for the analogue, are taken as an indication that the PMN chemical is probably nononcogenic or, in cases in which the analogy may have been doubtful, that the analogue was not appropriate. In either case, concern for potential oncogenicity is lessened as a result of mutagenicity data and a 2-year bioassay is generally not considered necessary.

In those instances in which the analogue chemical is inactive in short-term tests for mutagenicity, negative results for the PMN chemical do not alleviate concern for potential oncogenicity.

When an appropriate oncogenic analogue has been tested in the same assays as those required for the PMN chemical, this agent is generally included in the test as a positive control chemical.

Negative results for the PMN chemical, in the face of positive results for the analogue, are taken as an indication that the PMN chemical is probably nononcogenic.

Because of the cost of conducting a long-term bioassay, such a requirement is often interpreted by the regulated industry as a *de facto* ban. Chemicals subjected to the requirement for a long-term bioassay are often withdrawn by the submitter because they cannot support the cost of testing. The agency hopes that judicious and reasonable use of short-term testing will increase in the Sect. 5 process and that this increase in the use of short-term testing will reduce the number of chemicals subject to a bioassay.



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Quantitative Genetic Activity Graphical Profiles for Use in Chemical Evaluation

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A graphic approach, termed a Genetic Activity Profile (GAP), was developed to display a matrix of data on the genetic and related effects of selected chemical agents. The profiles provide a visual overview of the quantitative (doses) and qualitative (test results) data for each chemical. Either the lowest effective dose or highest ineffective dose is recorded for each agent and bioassay. Up to 200 different test systems are represented across the GAP. Bioassay systems are organized according to the phylogeny of the test organisms and the end points of genetic activity. The methodology for producing and evaluating genetic activity profiles was developed in collaboration with the International Agency for Research on Cancer (IARC). Data on individual chemicals were compiled by IARC and by the U.S. Environmental Protection Agency (EPA). Data are available on 343 compounds selected from volumes 1-53 of the IARC Monographs and on 115 compounds identified as Superfund Priority Substances. Software to display the GAPs on an IBM-compatible personal computer is available from the authors. Structurally similar compounds frequently display qualitatively and quantitatively similar profiles of genetic activity. Through examination of the patterns of GAPs of pairs and groups of chemicals, it is possible to make more informed decisions regarding the selection of test batteries to be used in evaluation of chemical analogs. GAPs provided useful data for development of weight-of-evidence hazard ranking schemes. Also, some knowledge of the potential genetic activity of complex environmental mixtures may be gained from an assessment of the genetic activity profiles of component chemicals. The fundamental techniques and computer programs devised for the GAP database may be used to develop similar databases in other disciplines.

Introduction

Data derived from short-term tests are usually interpreted according to the phylogenetic category of the test and the end point detected. Commonly studied end points include DNA damage, gene mutation, sister-chromatid exchange, micronuclei, chromosomal aberrations, aneuploidy, and cell transformation. Few short-term bioassays monitor more than one or two of these end points. Therefore, data from a variety of short-term tests are required to properly define the response profile of a given chemical agent.

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Garrett et al. (1984) developed a technique for presenting the quantitative genetic toxicology data for a chemical compound as a bar graph (genetic activity profile) in which test systems (identified by three-letter code words) are displayed along the x-axis and values corresponding to the doses employed in the tests are shown on the y-axis. The total data available from up to 200 different short-term bioassays for a compound are thus presented in a standardized format that allows rapid visualization of the genetic (or related) effects induced. The technique facilitates qualitative as well as quantitative assessments of genetic toxicity. Current procedures for the preparation and evaluation of genetic activity profiles (GAPs) are described by Waters et al. (1988a) in the context of their use by the International Agency for Research on Cancer (IARC).

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Methodology

The data set for a given chemical, consisting of a discrete set of tests and the doses required to induce responses in those tests, are presented in a bar graph as illustrated in Fig. 1.

The bar (profile lines) originating on the x-axis represent the tests plotted in either a phylogenetic or end point sequence. A three-letter code is used to identify the test system represented by each bar. Values on the y-axis are the logarithmically transformed lowest effective doses (LED) and highest ineffective doses (HID) tested. The term "dose," as used in this report, does not take into consideration length of treatment or exposure and may therefore be considered synonymous with concentration. The doses or concentrations used for all in vitro tests were converted to µg/ml, and those for in vivo tests to mg/kg bw per day. Because dose units are plotted on a log scale, differences in molecular weights of compounds do not greatly influence comparisons of GAPs.

Profile-line height (the magnitude of each bar) is a function of the LED or HID, which is associated with the characteristics of each individual test system, such as population size, cell-cycle kinetics, and metabolic competence. These characteristics and other factors make the detection limit of each test system different, therefore responses across the GAP will vary substantially. No attempt is made to adjust or relate responses in one test system to those of another.

Line-heights are derived as follows: For negative test results,

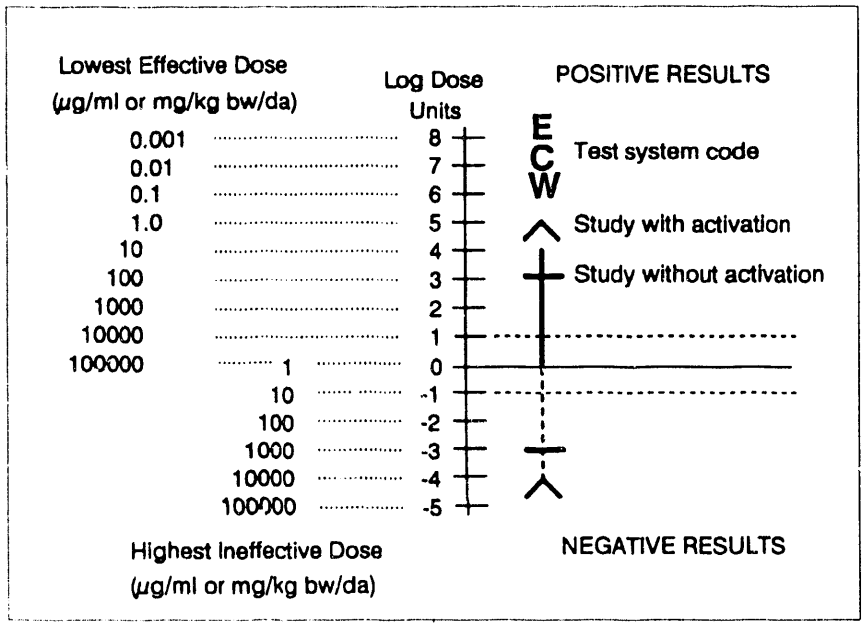

Fig. 1. A schematic representation of a Genetic Activity Profile (GAP) showing four studies for the test ECW (2 positive and 2 negative). The average LED of the majority call is indicated by a solid vertical bar. A dashed vertical bar indicates conflicting test results for the study. Note in cases where there are an equal number of positive and negative studies as here, the majority call is positive.

the highest dose tested without excessive toxicity is defined as the HID. If there is evidence of extreme toxicity, the next lower dose is used. A single dose yielding a negative result is considered equivalent to the HID. For positive results, the LED is recorded. If the original data have been analyzed statistically by the author, the dose recorded is that at which the response was significant ($p < 0.05$). If the data were not analyzed statistically, the dose required to produce an effect is estimated as follows: When a dose-related positive response is observed with two or more doses, the lower of the doses is taken as the LED; a single dose resulting in a positive response is considered equivalent to the LED.

To accommodate both positive and negative responses on a continuous scale, doses are transformed logarithmically so that effective (LED) and ineffective

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(HID) doses are represented by positive and negative numbers, respectively. The logarithmic dose unit [$LDU_{(ij)}$] for a given test system i and chemical j is represented by the expressions:

$LDU_{(ij)} = -\log_{10}(\text{dose})$, for HID values; $LDU \leq 0$

$LDU_{(ij)} = 5 - \log_{10}(\text{dose})$, for LED values; $LDU \geq 0$

These simple relationships define a dose range of 0 to –5 logarithmic units for ineffective doses (1 to 100,000 µg/ml or mg/kg bw/day) and 0 to +9 logarithmic units for effective doses (100,000 to 0.0001 µg/ml or mg/kg bw/day). A scale illustrating the LDU values is shown in Fig. 1. Negative responses at doses <1 µg/ml (mg/kg bw/day) were set equal to 1. Effectively, an LED value >100,000 or an HID value <1 produces an LDU = 0; no quantitative information is gained from such extreme values. Levels of log dose units between 1 and –1 define a "zone of uncertainty" in which positive results are reported at very high doses (10,000 to 100,000 µg/ml or mg/kg bw/day), and negative results are reported at relatively low dose levels (1 to 10 µg/ml or mg/kg bw/day).

All dose values are plotted for each assay using either a bar (-) for results obtained in the absence of an exogenous metabolic system or a caret (^) for those obtained in the presence of an exogenous metabolic system. When all results for a given assay are either positive or negative, the geometric mean of the responses is plotted as a solid line; when conflicting data are reported for the same assay (i.e., both positive and negative results) the majority data are shown with a solid line and the minority data with a dashed line (drawn to the extreme response). In the few cases in which the numbers of positive and negative results are equal, the solid line is drawn in the positive direction and the negative response is indicated with a dashed line, drawn from the origin to the extreme negative LDU (Fig. 1).

The three-letter code words representing the commonly used tests were originally defined by the GENE-TOX program of the U.S. Environmental Protection Agency (EPA) (Waters 1979; Waters and Auletta 1981). These codes have been systematically redefined and expanded to facilitate inclusion of additional tests in the future (Waters et al. 1988).

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Evaluation of Genetic and Related Effects

IARC has employed the GAP methodology (Waters et al. 1988) in evaluating genetic and related effects of suspected human carcinogens in *IARC Monographs* Supplement 6 (IARC 1987a) and in vols. 36, 39, 41, 44 (IARC 1985a, 1985b, 1986, 1988b), and 46-53 (IARC 1989b, 1989c, 1990a, 1990b, 1990c, 1991a, 1991b, 1991c). Figure 2 illustrates the procedure currently employed by the IARC as it relates to the GAP data base.

The International Agency for Research on Cancer employs the GAP methodology in evaluating genetic and related effects of suspected human carcinogens in IARC Monographs.

Nesnow (personal communication) has recently completed a personal computer (PC) dBase version of the data on carcinogenicity contained in *IARC Monographs* Supplement 7 (IARC 1987b) and IARC Monograph Vols. 43–49 (IARC 1988a, 1988b, 1989a, 1989b, 1989c, 1990a, 1990b, 1991a, 1991b,

PRIOR TO THE IARC MONOGRAPH WORKING GROUP MEETING

1. IARC selects compounds and completes literature search
2. Working subgroup members review literature for individual compound(s)
3. Subgroup member prepares
   (a) Written summary
   (b) Summary table
   (c) Data listing
4. Drafts of data and summaries are sent to IARC

DURING THE IARC MONOGRAPH WORKING GROUP MEETING

5. Genetic and related effects subgroup convenes
6. Data summaries and tests are verified for each compound
7. Final drafts are submitted to Working Group for review
8. Data tables and summaries are sent to EPA/GTD for dose verification
9. Genetic activity profiles and data listings are prepared and sent to IARC

Fig. 2. The current process of chemical selection and review of data on genetic and related effects used in the preparation of genetic activity profiles for *IARC Monographs*.

1991c). Most of these agents are included in the GAP data base [derived from *IARC Monographs* Supplement 6 (IARC 1987) and Monograph Vols. 46-49 (IARC 1989b, 1989c, 1990a, 1990b)]. Therefore, these two databases can be used to examine retrospectively the usefulness of short-term tests for the prediction of carcinogenicity and the relationship between specific genetic end points or assays and carcinogenicity.

PC Version of the GAP Data Base - Version 3.0

Copies of software for IBM-compatible PCs to display and search GAPs are available from the authors. Computer programs require the following minimum configuration: PC using Intel 8086 chip (PC XT) with 640-kb memory, a hard-disc drive, an enhanced graphics card (EGA or VGA), a high-resolution color monitor, and DOS Version 3.2 or higher.

Generally, an Intel 80286 (PC AT) computer is preferred because data processing and graphics display are faster than with the 8086 computer. Optional devices used for data and graphic output include a line printer and plotter. Alternatively, a laser printer or equivalent can be used to print the Hewlett Packard (HPGL) plotter files using additional software.

The GAP software is distributed on a single high density, 5.25 in. floppy disk containing the programs, data, and GAP bibliography.

Executable programs are archived on the program disk and are compiled from programs

Copies of software for IBM-compatible PCs to display and search GAPs are available from the authors.

written in Turbo Pascal. During installation of the programs, the necessary directory and subdirectories are created. The installed programs and data use approximately 1.2 Mb of disk space.

The bibliography of the GAP data is also in an archived file. The file requires 0.7 Mb of disk space; however, the bibliography is not necessary to operate the GAP programs, and it may be deleted and reinstalled as needed.

The database consists of two data sets, "IARC" and "EPA." The IARC data set contains data on 343 agents published in Supplement 6 (IARC 1987) and in Volumes 46-53 of the *IARC Monographs* (IARC 1989b, 1989c, 1990a, 1990b, 1990c, 1991a, 1991b, 1991c). The EPA data set contains data on 115 agents assembled for the Genetic Toxicology Division of EPA (Waters et al. 1990a). A list of the individual projects included in each data set may be viewed using the GAP computer program. A data subdirectory is provided for users to enter their own data.

The main program menu of GAP Version 3.0 offers the following selections: agents, profiles, data listings, modify data, short citations, and additional information.

"Agents" provides options to list the available projects, CAS numbers and agent names. Another menu allows ordering of the list by any of the three options.

"Profiles" provides graphic display of the short-term test data on selected agents. A menu is used to select the sequence of test codes, either in phylogenetic order of organisms (i.e., prokaryotes, lower eukaryotes, etc.) or in test end-point order (i.e., DNA damage, gene mutation, etc.). Individual test codes may be examined to determine the source citations by using the GAP program zoom-in features.

"Listings" produces a listing of the data in either phylogenetic or end-point order and may be directed to the PC screen, a printer, or a data file.

"Modify data" is used to add, change, or delete agents or test results (e.g., test codes, results, doses, and reference numbers).

"Short citations" permits searching the literature citation information for approximately 6000 short citations contained in the GAP database. The citation information includes the citation number (LITNR), the Environmental Mutagen Information Center (EMIC) accession number, and a short citation (consisting of the last names of up to three authors, the first page number, and the year of the publication). The citation information may be searched by author or by EMIC number to determine if a citation is present. Short citations also may be added to the file and are automatically assigned citation numbers.

"Additional information" includes three-letter test code definitions, the scale of log-dose units used in the profiles, information on the dose conversions, and tables listing projects for both the EPA and IARC data sets.

The bibliography of the GAP data is also in an archived file.

The citation information may be searched by author or by EMIC number.

Some Applications of the GAP DataBase

1. Comparative Evaluation of Genetic Activity Profiles Using Computer-Based Profile Matching Techniques.

Where an adequate number of the same test has been used to evaluate two or more chemicals, it is possible to use the mainframe computer to select matching "pairs" of GAPs. This computer-based pairwise matching process may be extended to all chemicals in the database. The pilot applications of this procedure to EPA databases on known or suspected human carcinogens (Garrett et al. 1984) and on pesticide chemicals (Garrett et al. 1986) have demonstrated that structurally similar compounds frequently display qualitatively and quantitatively similar profiles of genetic activity. This implies that the GAP database should be of considerable utility in structure activity relationship (SAR) investigations and in selecting tests and batteries of tests to be applied to chemicals that have not been fully evaluated (Waters et al. 1988b).

Through the examination of the patterns of GAPs of pairs and groups of chemicals, it is possible to make informed decisions regarding the selection of test batteries to be used in the subsequent evaluation of structurally similar chemicals. The approach draws on the information in the entire database and may be linked to computer systems that model the molecular properties of the chemicals under evaluation (Richard et al. 1989). This comparative information can enhance our understanding of the relationships between genetic and related activity in short-term tests and molecular properties of structurally related chemicals and thus contribute to our knowledge of the mechanisms of complex processes such as carcinogenesis.

It is possible to make informed decisions regarding the selection of test batteries to be used in the subsequent evaluation of structurally similar chemicals.

2. Testing and Evaluation of Complex Mixtures

A recent application of GAPs is in the testing and evaluation of complex mixtures (Waters et al. 1990b). Some knowledge of the potential genetic activity of a complex environmental mixture may be gained from an assessment of the genetic activity of its component chemicals. This requires information on the chemical components and composition of the mixture. For example, the Atmospheric Chemical Compound database developed by Graedel et al. (1986) contains information on chemical structures, properties, detection methods, and sources of chemicals found in ambient air. The GAP database provides a computer-generated graphic representation of genetic bioassay data as a function of dose. Using the two databases together, information on the quantity of an individual chemical present within a mixture may be related to the quantity (LED) of the chemical required to demonstrate a positive response in one or more genetic bioassays. Quantitative information on the carcinogenic potency of each individual compound [toxicity dose for 50% of a population (TD_{50}) value] may also be related to the quantity present in the mixture or mixture fraction. In turn, the quantity of the chemical in the complex mix-

The GAP database provides a computer-generated graphic representation of genetic bioassay data as a function of dose.

ture to which humans are exposed may be estimated and used to calculate the percent human exposure dose/rodent potency dose (HERP) for the chemical (Gold et al. 1984, 1987; Gold 1991). By using an additivity assumption, for example, an estimate of potential carcinogenic hazard for the mixture may be calculated based on the HERP indices for the known chemical components. This conceptual approach is limited by the relatively small number of chemicals identified in complex mixtures for which genetic toxicology and animal cancer data exist.

3. Weight-of-Evidence Ranking Schemes

Committee I of the International Commission for Protection Against Environmental Mutagens and Carcinogens (ICPEMC) has been involved for several years in the development of a computer-based methodology to assess the evidence from short-term genetic tests that a chemical is a mutagen (Lohman et al. 1990). The evaluative approach selected by ICPEMC Committee I is based on a "weighted test" scoring system that provides a relative ranking of genotoxic potential. Input data for this ranking methodology have been obtained from the GAP database (Brusick 1991). The results of the application of the Committee I ranking scheme are to be compared by ICPEMC with results obtained by applying the carcinogenicity ranking scheme of Nesnow (1984, 1991).

4. Development of Other Data-Bases

The fundamental techniques and computer programs devised for the GAP database may be used to develop similar databases in genetic toxicology and in other disciplines. Dearfield et al. (1991) have described the application of the GAP methodology to the data base being constructed by the EPA Office of Pesticide Programs. Kavlock et al. (1991) have successfully used the approach and modified computer programs to assemble graphic activity profiles and corresponding data listings for several developmental toxicants.

Future Directions

A useful application of the GAP database in the future will involve computer-based profile matching techniques (see 2. above) with weight-of-evidence ranking schemes (see 4. above) to subset chemicals that act similarly (i.e., have similar GAPs). Correlative structure-activity approaches can then be used more effectively to identify the substructural elements of chemicals that are responsible for particular biological responses to suggest biologically plausible mechanisms of action (Waters 1990).

Correlative structure-activity approaches can be used to identify the substructural elements of chemicals responsible for particular biolog'cal responses so as to suggest biologically plausible mechanisms of action.

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The TSCA Interagency Testing Committee's Approaches to Screening and Scoring Chemicals and Chemical Groups: 1977-1983

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This paper describes the TSCA Interagency Testing Committee's (ITC) approaches to screening and scoring chemicals and chemical groups between 1977 and 1983. During this time the ITC conducted five scoring exercises to select chemicals and chemical groups for detailed review and to determine which of these chemicals and chemical groups should be added to the TSCA Section 4(e) Priority Testing List.

Introduction

The TSCA Interagency Testing Committee (ITC) was created under Section 4(e) of the Toxic Substances Control Act (TSCA) after six years of intense Congressional debate over proposed toxic substances control legislation. Congress directed 8 U.S. government organizations to appoint members to the ITC for 4-year terms and established specific qualifications for membership. Congress mandated that one member each shall be appointed by the:

Administrator of the U.S. Environmental Protection Agency (EPA),

Secretary of Labor (the Occupational Safety and Health Administration, OSHA),

Chairman of the Council on Environmental Quality (CEQ),

Director of the National Institute for Occupational Safety and Health (NIOSH),

Director of the National Institute of Environmental Health Sciences (NIEHS),

Director of the National Cancer Institute (NCI),

Director of the National Science Foundation (NSF), and

Secretary of the Department of Commerce (DOC).

Since the ITC's first meeting on February 5, 1977, 10 U.S. government organizations with experience in chemical testing have participated as Liaison Members:

Department of Defense (DOD),

Department of the Interior (DOI),

Food and Drug Administration (FDA),

Consumer Product Safety Commission (CPSC),

Department of Agriculture (USDA),

National Toxicology Program (NTP),

National Library of Medicine (NLM),

Agency for Toxic Substances and Disease Registry (ATSDR),

Department of Transportation (DOT), and the

Six years of intense Congressional debate led to creation of the TSCA Interagency Testing Committee.

U.S. International Trade Commission (USITC).

Congress directed the ITC to: 1) develop the **TSCA Section 4(e)** ***Priority Testing List*** within 9 months of TSCA's effective date, 2) use 8 statutory criteria to prioritize testing for about 60,000 existing chemicals, 3) determine the order in which the Administrator of the EPA should implement the testing recommendations for chemicals and chemical groups on the **TSCA Section 4(e)** ***Priority Testing List***, 4) revise the **TSCA Section 4(e)** ***Priority Testing List*** at least every six months and 5) facilitate coordination of chemical testing among the U.S. Government organizations represented on the ITC.

Developing Initial Lists

Initial Lists of chemicals and chemical groups were developed from lists of chemicals referred to the ITC by Statutory and Liaison organizations (Table 1). These chemicals and chemical groups were referred to the ITC because of concerns about the adequacy of test data. Developing the Initial List was the first stage of selecting chemicals by the ITC (Fig. 1).

The ITC's First Scoring Exercise was conducted in 1977. At that time, there was no TSCA Inventory of commercially-available existing chemicals and chemical

Chemicals were included in the ITC's Initial Lists because U.S. regulatory agencies had concerns about test data adequacy.

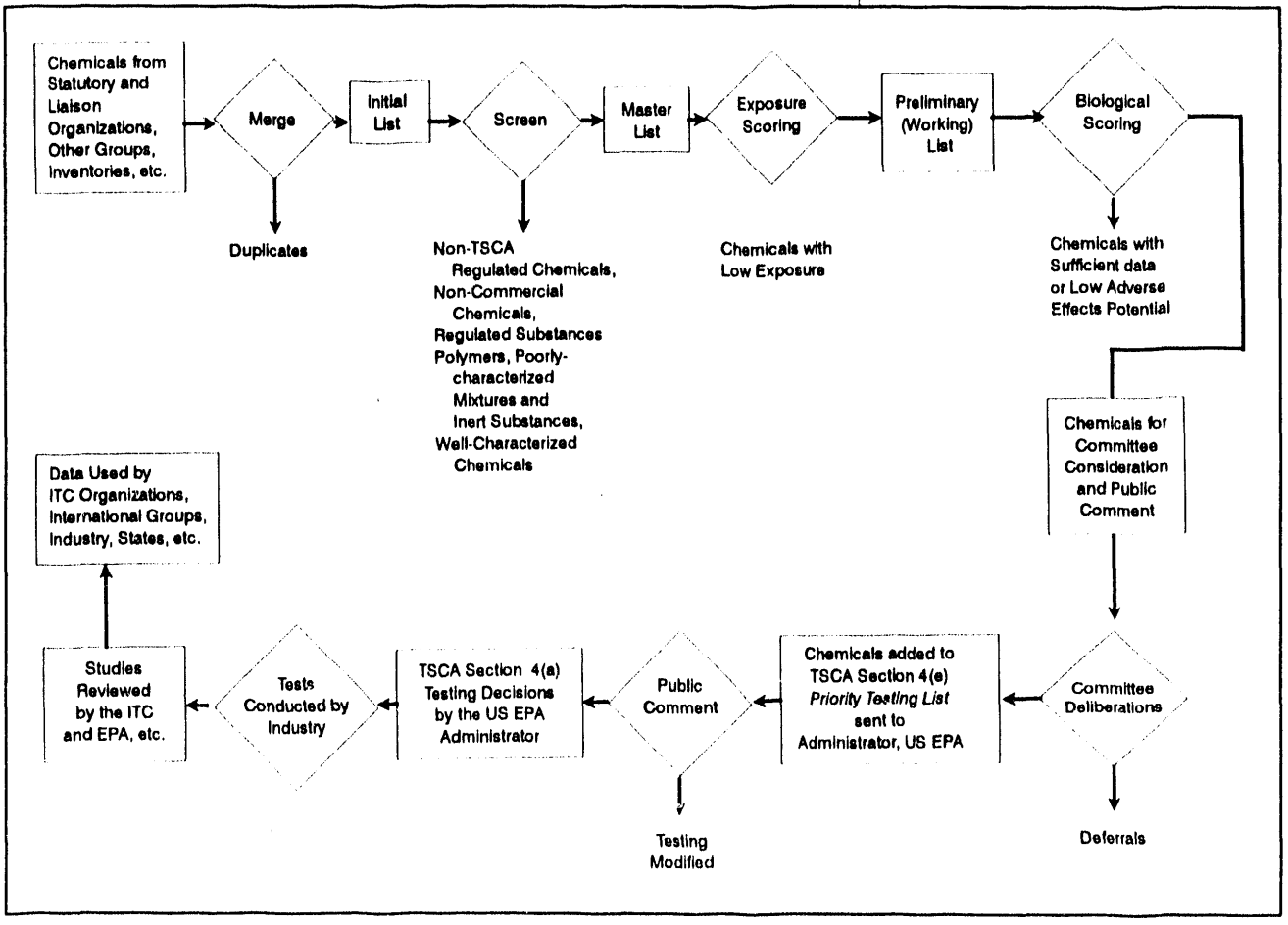

Fig. 1. The TSCA Section 4(e) Interagency Testing Committee process for screening, scoring and selecting chemicals and chemical groups: 1977-1983.

Table 1. Sources of Chemicals and Chemical Groups for the ITC's First Scoring Exercise

	Source	Chemicals
DOI	Fish and Wildlife Hazards	174
EPA	Priority Pollutants	129
EPA	Air Contaminants	337
EPA	Estuarine Pollutants	9
EPA	Office of Toxic Substance Priority Chemicals	162
FDA	Potential Carcinogens	88
NCI	Substances for Cancer Bioassays	372
NIOSH	Criteria Document Substances	127
NIOSH	Substances with Potential Occupational Exposure	500
NSF	Environmental Contaminants	80
OSHA	Suspected Carcinogens	116
ACGIH	Threshold Limit Value Substances	570
CANADA	Environmental Contaminants of Concern to Canada	160

groups. Estimates of the number of chemicals and mixtures subject to TSCA ranged from 10,000 to 100,000. All of these were within the statutory purview of the ITC. TSCA listed a number of factors related to chemicals and chemical groups that the ITC had to consider before recommending testing: 1) quantities manufactured, 2) quantities released to the environment, 3) numbers of individuals exposed and duration of exposure, 4) extent of human exposure, 5) structural relationships to known toxic substances, 6) available toxicity data, 7) reliability of test data to predict hazard and 8) availability of testing facilities. The ITC used these factors and some nonstatutory factors such as concerns for adequacy of data to develop a tiered process for selecting chemicals and chemical groups for testing consideration. The first step in this process involved developing an Initial List of chemicals for consideration (Walker and Brink 1989).

To develop the Initial List, the ITC focused its attention on substances that satisfied the TSCA Section 4(e) statutory factors and some nonstatutory factors such as concerns for adequacy of data. The ITC chose to limit its Initial List to chemicals or groups which had been identified in previous reviews by ITC's Statutory or Liaison organizations as being of concern because of potential adverse effects on human health or the environment or as having large production volumes and a potential for substantial human exposure or environmental release.

In addition to referrals from Statutory and Liaison organizations, the Initial List also included 570 chemicals and

Attention was focused on chemicals that have potential adverse effects on human health or the environment.

chemical groups for which the American Conference of Government Industrial Hygienists (ACGIH) had established Threshold Limit Values and 160 chemicals and chemical groups of concern to the Canadian government. After removing duplicates, the Initial List contained approximately 3,600 chemicals and chemical groups (Table 2).

The ITC's Second Scoring Exercise was conducted in 1978. At that time, there was still no TSCA Inventory. The chemicals for consideration included those described above (the sources of which are listed in Table 1) plus chemicals included in the Environmental Mutagen Information Center (EMIC) and the Environmental Teratology Information Center (ETIC) databases. This list was screened against the list of synthetic organic chemicals compiled annually by the USITC. This screening produced an Initial List of 1571 chemicals (Table 2).

The ITC's Third Scoring Exercise was conducted in 1980. The TSCA Inventory was available for the first time and was used as the sole source of chemicals for the Third Scoring Exercise. Chemicals in the public portion of the Inventory with minimum aggregate production volumes equal to or greater than 2 million pounds were included in an

The Initial List contained about 3600 chemicals and chemical groups of concern to ITC's Statutory and Liaison organizations.

Table 2. Sources and Numbers of Chemicals Processed Through the ITC's First, Second, Third, Fourth, and Fifth Scoring Exercises

Scoring Exercise	Year	Sources of Chemicals	Number of Chemicals				
			Initial List	Master List	Preliminary List	Biological Scoring	Detailed Review
1	1977	Listed in Table 1	3600	1700	330[a]	451	80
2	1978	Table 1, EMIC and ETIC databases and USITC list of synthetic organic chemicals	1571			252	
3	1980	TSCA Inventory chemicals with annual production volumes ≥2 million pounds	1877			215	107
4	1981	TSCA Inventory chemicals with annual production volumes ≥1 million pounds, STORET, FDA fish contaminants, CPSC database and mixtures removed from 3rd Scoring Exercise	2755			213	75
5	1983	TSCA Confidential Business Information Inventory and Public Inventory chemicals ≥1 million pounds and not in previous scoring exercises, 820 previously scored chemicals, 257 previously deferred chemicals, 46 analogs of known carcinogens, 6 chemicals from Canada's Environmental Protection Service, 5 chemicals from CPSC, 4 chemicals from DOI/FWS, and 11 chemicals from EPA	3370	471	214[b]	214	82

[a]Includes about 290 chemicals and 40 chemical groups.
[b]Also referred to as a Working List.

Initial List of 1877 chemicals (Table 2).

The ITC's Fourth Scoring Exercise was conducted in 1981. Chemicals in the public portion of the TSCA Inventory with minimum aggregate production volumes equal to or greater than 1 million pounds were selected for consideration as were chemicals from several other sources including cumulative supplements to the TSCA Inventory, EPA's STORET database (75 chemicals), FDA's list of food (fish) contaminants (38 chemicals), the Auerbach Consumer Product Database from CPSC (1320 chemicals) and chemical mixtures removed from consideration during the Third Scoring Exercise (52 chemical mixtures). Combining these lists and removing 1877 chemicals considered during the Third Scoring Exercise and 244 duplicates produced an Initial List of 2755 chemicals (Table 2).

The ITC's Fifth Scoring Exercise was conducted in 1983. The confidential business information (CBI) portion of the TSCA Inventory was used for the first time. Chemicals in the public and CBI portions of the TSCA Inventory with minimum aggregate production volumes equal to or greater than 1 million pounds that were not considered during previous scoring exercises (1765 chemicals) were selected for consideration as were chemicals from several other sources including 820 previously scored chemicals that were not studied in detail, 257 previously deferred chemicals, 46 analogs of known carcinogens, 6 chemicals of concern to Canada's Environmental Protection Service, 5 chemicals recommended by CPSC, 4 chemicals recommended by the DOI's Fish and Wildlife Service, and 11 chemicals recommended by the EPA's Office of Toxic Substances. This Initial List contained 3370 chemicals (Table 2).

Chemicals were added from such sources as the FDA's list of food contaminants and Canada's Environmental Protection Service.

Developing Master Lists

Master Lists of chemicals and chemical groups were generated from Initial Lists by deferring chemicals that were considered to be non-TSCA regulable or not commercially significant. This was the second stage of selecting chemicals by the ITC (Fig. 1).

The Master List was developed from the Initial List from the First Scoring Exercise by deferring a number of substances having pesticide, food additive, or drug uses, all of which are regulated under other Federal statutes and are exempted from regulation under TSCA. To identify them, the Initial List was compared with lists of pesticides prepared by the EPA and lists of food additives and drugs prepared by the FDA, using Chemical Abstracts Service (CAS) Registry Numbers. Since some entries on source lists did not include CAS numbers, manual purging was done. Consideration was also given to the fact that a substance used as a pesticide, food additive or drug may also have other uses that are subject to the authority of TSCA. Since pesticides, food additives, and drugs are generally produced in limited quantities, substances identified as such but having annual production volumes over 10 million pounds were considered likely to have TSCA uses as well and were retained on the Master List for further review of

The Initial List was compared with lists of pesticides prepared by the EPA and lists of food additives and drugs prepared by the FDA.

their uses. Substances identified as pesticides, food additives, or drugs but known to have TSCA uses were also retained.

The resulting Master List was reduced further by the elimination of chemicals which were judged not likely to be in commercial production. This was accomplished by comparing the file against EPA's Candidate List of Chemical Substances, prepared by the Office of Toxic Substances (dated April 1977). The basis of comparison for this purge was also an assigned CAS number. Consequently, this purge did not affect those chemicals on source lists for which no CAS number was given. In an attempt to eliminate substances which were not in commercial production, the following rule was adopted: any substance not identified by a CAS number which appeared on the NIOSH Registry and on none of the other source lists was judged not likely to be in commercial production. This decision was based on the fact that the NIOSH Registry lists any substance for which toxic effects have been reported, including research chemicals. A scan of the substances eliminated by the application of this rule demonstrated its usefulness: few of the purged substances were recognized to be in commercial production. As a result of the purges described above, about 230 pesticides, 40 food additives, 270 drugs, 450 non-commercial chemicals with CAS numbers and 960 non-commercial chemicals without CAS numbers were removed from the Initial List, creating a Master List of approximately 1700 substances (Table 2).

Historical records on the development of Master Lists during the second, third and fourth scoring exercises could not be located.

The Master List prepared from the Fifth Scoring Exercise Initial List was reduced to 2914 chemicals by eliminating duplicates. The list of 2914 chemicals was further reduced to 471 chemicals by removing 329 well-studied chemicals, 102 polymers from innocuous monomers, 950 poorly-characterized mixtures of variable indefinite or unknown structure, 387 chemicals under review elsewhere, 316 inorganic and organic chemicals of known or suspected low hazard potential, 189 chemicals produced in less than 100,000 pounds per year, and 170 chemicals of low toxicological concern (Table 2).

The Master List was reduced by eliminating chemicals judged not likely to be in commercial production.

Exposure Scoring of Chemicals

Details of exposure scoring as they were developed for the First Scoring Exercise are available in Appendix A.

The ITC initially considered applying all 8 statutory factors to the chemicals and chemical groups in the Master List, but concluded that it would be impossible to collect and review all this information considering the limitations of the available information systems, the number of professional judgements to be made and the statutory time limits for submitting the ITC's First Report to the EPA Administrator. The ITC eliminated consideration of factors 5-7 (structural relationships to known toxic substances, available toxicity data, and reliability of test data to predict hazard) because it would be time consuming to consider

It would be impossible for the ITC to collect and review all statutory-mandated information considering resource limits, limitations of available information systems, and the statutory time limits for submitting reports to the EPA Administrator.

factors which to a certain extent had been used to select substances for the Initial List. The ITC reviewed surveys conducted by the Society of Toxicology and the Department of Health Education and Welfare and the plans of FDA's National Center for Toxicological Research and decided that statutory factor number 8 (availability of testing facilities) was adequate for chemicals likely to be added to the ITC's First Report (ITC 1977). In their 2nd and 3rd Reports, the ITC recommended conducting a more comprehensive survey of available facilities for conducting health and environmental tests (ITC 1978 a,b).

Based on these considerations, the ITC used statutory factors 1-4 (quantities manufactured, quantities released to the environment, numbers of individuals exposed, duration and extent of human exposure) to score chemicals on the Master List. Using a combination of published data and professional judgement, the ITC attempted to score each of the chemicals and chemical groups in the Master List for each of these factors. Information on chemical uses was critical for the development of scores for environmental release and general population exposure. This information was available for only about 700 of the 1700 chemicals and chemical groups on the Master List.

Historical records on exposure scoring of chemicals on Master Lists during the second, third and fourth scoring exercises could not be located.

Exposure scoring of the chemicals in the Master List from the Fifth Scoring Exercise used methods similar to those described for ITC's First Scoring Exercise (ITC 1977).

Developing Preliminary Lists

Preliminary Lists of chemicals and chemical groups were generated from Master Lists by exposure scoring and were the third stage of selecting chemicals by the ITC (Fig. 1).

Exposure scoring reduced the Master List from the First Scoring Exercise to a Preliminary List that contained approximately 290 chemicals and 40 chemical groups (Table 2). These chemicals and chemical groups as well as examples of chemicals in these chemical groups were made publicly available by the ITC in two *Federal Register* notices that were published June 17, 1977 (42 FR 30531) and August 11, 1977 (42 FR 40756).

In selecting the approximately 330 chemicals and chemical groups included on the Preliminary List, the ITC considered all of the scored substances and eliminated from consideration a number of them which in the ITC's professional judgment were found to be:

a. Under stringent regulation or of lower priority for the ITC's purposes because their hazard was reasonably well characterized (e.g., vinyl chloride and mercury);

b. Essentially inert materials (e.g. certain polymers) or substances reasonably well characterized as having low toxicity (e.g., methane);

Information on chemical uses was critical for developing scores for environmental release and general population exposure.

Exposure scoring reduced the Master List to a Preliminary List containing about 290 chemicals and 40 chemical groups.

c. Covered by testing requirements under food, drug and cosmetic or pesticide legislation (e.g., citric acid); or

d. Certain natural products (e.g., asphalt) whose consideration should be deferred pending better characterization for testing purposes.

In addition to the scored substances on the Preliminary List, the ITC also considered the unscored substances from the Master List and a number of additional substances recommended by ITC Members.

In reviewing substances for possible inclusion on the Preliminary List, the ITC also considered the desirability of grouping substances into categories. In several cases the ITC grouped chemically-related substances from the Master List while in other cases the ITC retained groups which had already appeared in one of the source lists. About 15% of the entries on the Preliminary List were substances categories.

Historical records on the development of Preliminary Lists during the second, third and fourth scoring exercises could not be located.

Exposure scoring of the 471 chemicals in the Master List from the Fifth Scoring Exercise produced a Preliminary List of 214 chemicals (Table 2).

Biological Scoring of Chemicals on Preliminary Lists

Details of the criteria that were used to score chemicals for biological effects are available in Appendix B. Biological scores were developed by experts. The number of chemicals that were scored for biological effects during each scoring exercise is listed in Table 2.

The ITC used these biological scores as part of the effort to rank chemicals for consideration. The ITC also reviewed a list of those substances evaluated by the scorers which were known or might be anticipated to have additional adverse health or environmental effects as a result of contaminants appearing in the commercial product or degradation products of the substance under consideration.

The Committee also considered the desirability of grouping substances into categories.

The ITC's selection of substances for more detailed review also reflected the effect of concerns by the Statutory or Liaison organization that referred the substance to the ITC (Table 2).

In keeping with the statutory guidance provided the ITC in Section 4(e)(1)(A) of TSCA, the ITC focused attention on substances suspected of causing cancer, gene mutations, or birth defects. This emphasis was reflected not only in the ITC's consideration of individual substances and categories, but also in its structuring of the review process, since these effects were scored individually and, in effect, received greater attention than did other effects scored in groups (e.g., other toxic effects or ecological effects).

The ITC used biological scores as part of the effort to rank chemicals for consideration.

Selecting Chemicals for ITC Consideration and Public Comment

The ITC provides many opportunities for the public to comment on ITC procedures and the chemicals and chemical groups

that are selected for review by all Statutory and Liaison organizations (Fig. 1). For example, all 30 (as of May 1992) ITC Reports to the EPA Administrator have been published in the *Federal Register* and public comments on the testing recommended in these Reports have been solicited and considered.

Before the ITC added any chemicals or chemical groups to the ***Priority Testing List***, the Preliminary List from the First Scoring Exercise and a background document describing its development, was published by the ITC in July, 1977. The ITC published 2 notices in the *Federal Register* (42 FR 30531 and 42 FR 40756) announcing the availability of the List and background document and requesting public comment. Comments were specifically requested on:

a. Methodology used by the ITC in developing the Preliminary List;

b. Substances not appearing on the Preliminary List which commentors might recommend for consideration by the ITC and the commentor's reasons for the recommendation;

c. Substances appearing on the Preliminary List which commentors might recommend that the ITC not consider further and the reasons for that recommendation; and

d. Need for and relative priority of testing of the substances being considered by the ITC.

Comments on the Preliminary List were received from about 65 industrial firms, trade associations, environmental organizations, government agencies, and individuals. About two-thirds of the commentors recommended deletion of one or more substances or categories appearing on the Preliminary List, while four commentors recommended additional substances for the ITC's consideration. About one-fifth of the comments focused on the methodology employed by the ITC in developing the Preliminary List and about one-third included comments on other issues related to the ITC's activities. Such issues were: the use of categories in the ITC's recommendations to EPA, documentation of the ITC's reasons for its decisions with respect to specific substances, and provision of opportunity for public comment on the ITC's action.

Focus was on substances suspected of causing cancer, gene mutations, or birth defects.

Public comments on the Preliminary List were reviewed by the ITC and considered in the development of the ITC's initial recommendations. Four of the seven additional substances recommended by commentors were added to the Preliminary List for consideration in selecting substances and categories for detailed review. Because of the large number of comments recommending deletions of substances from the ITC's consideration and the limited time available under the statutory deadline, pertinent comments were considered on a substance-by-substance or category-by-category basis during the ITC's review of preliminary dossiers and consideration of reasons for and against recommending testing. Comments on the ITC's methodology were reviewed and considered in subsequent activities of the ITC. In the ITC's judgment, the recommended changes in methodology would not, if

Many opportunities were provided for the public to comment on procedures and chemicals.

implemented, alter its initial recommendations. Comments dealing with use of categories, documentation of the ITC's reasons for actions, and other more general issues were also reviewed and considered in the development of the ITC's recommendations.

During the First Scoring Exercise, public comments were solicited on 80 chemicals that were selected for detailed review (Table 2).

During the Second Scoring Exercise, public comments were solicited on the 451 chemicals that were scored for biological effects (Table 2).

During the Third Scoring Exercise, the 215 chemicals that were scored for biological effects were reduced to a list of 107 chemicals that were published in the October 7, 1980 *Federal Register* (43 FR 66506) for public comments (Table 2).

During the Fourth Scoring Exercise, the 213 chemicals that were scored for biological effects were reduced to a list of 75 chemicals that were published in the February 25, 1982 *Federal Register* (47 FR 8244) for public comments (Table 2).

During the Fifth Scoring Exercise, the 214 chemicals that were scored for biological effects were reduced to a list of 82 chemicals that were published in the November 9, 1983 *Federal Register* (48 FR 51519) for public comments (Table 2).

Developing And Revising The TSCA Section 4(e) Priority Testing List

Developing and revising the TSCA Section 4(e) ***Priority Testing List*** has been previously described by Walker (1993a). All the ITC Reports containing the original as well as revisions to the ***Priority Testing List*** as a result of selecting chemicals from the First through Fifth Scoring Exercises are listed below in the references. Most of the chemical fate, bioconcentration and ecological effects testing has been previously described (Walker 1990a,b, 1991b, 1993b).

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ITC. TSCA Interagency Testing Committee Report to the Administrator; Receipt of Report and Request for Comments Regarding *Priority Testing List* of Chemicals:

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1978a. Second Report. *Federal Register* **43**:16684-88, April 19, 1978.

1978b. Third Report. *Federal Register* **43**:50630-35, October 10, 1978.

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1979b. Fifth Report. *Federal Register* **44**:70664-74, December 7, 1979.

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1981a. Eighth Report. *Federal Register* **46**:28138-44, May 22, 1981.

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1982a. Tenth Report. *Federal Register* **47**:22585-96, May 25, 1982.

1982b. Eleventh Report. *Federal Register* **47**:54625-44, December 3, 1982.

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1983b. Thirteenth Report. *Federal Register* **48**:55674-84, December 14, 1983.

1984a. Fourteenth Report. *Federal Register* **49**:22389-407. May 1984.

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1985a. Sixteenth Report. Federal *Register* **50**:20930-39, May 21, 1985.

1985b. Seventeenth Report. *Federal Register* **50**:47603-12, November 19, 1985.

1986a. Eighteenth Report. *Federal Register* **51**:18368-75, May 19, 1986.

1986b. Nineteenth Report. *Federal Register* **51**:41417-32, November 14, 1986.

1987a. Twentieth Report. *Federal Register* **52**:19020-26, May 20, 1987.

1987b. Twenty-first Report. *Federal Register* **52**:44830-37, November 20, 1987.

1988. Twenty-second Report. *Federal Register* **53**:18196-210, May 2, 1988.

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Appendix A— Exposure Scoring

Exposure scoring was similar for the ITC's first, second, third, fourth and fifth scoring exercises. The factors used to score chemicals for exposure during the first scoring exercise are described below.

Factor 1: Production

Annual production data were collected from a number of sources:

a. EPA's Air contaminants (Table 1)

b. EPA study of industrial data on 650 candidate chemicals for testing

c. EPA Office of Research and Development's chemical production data on about 140 chemicals

d. Synthetic Organic Chemicals, United States Production and Sales. 1975. United States International Trade Commission

e. Stanford Research Institute 1975 Chemical Economics Handbook

f. *Chemical and Engineering News*: Vol. 52, No. 51, 12/23/74; Vol. 55, No. 18, 5/2/77; Vol. 55, No. 24, 6/13/77

The Factor 1 score assigned to a chemical was the common logarithm of the highest annual pro-

All ITC reports containing the original as well as revisions to the list are in the references for this paper.

duction value (in millions lbs/yr) found in any of the above sources. If an annual production value was not available for a chemical in any of these sources, a Factor 1 score of –0.5229 (corresponding to an assumed annual production of 300,000 pounds) was assigned.

Factor 2: Quantity Released to the Environment

The quantity of chemical released to the environment was scored on a scale from 0 to 3 as follows:

Release quantity and persistence, were taken as an indication of the environmental burden posed by the chemical.

Score	Release Rate	Estimate Based on Uses
3	>30 percent	Mostly dispersive uses
2	3 to 30 percent	Some dispersive uses
1	0.3 to 3 percent	Few dispersive uses; or primarily industrial chemical with propensity for leaks
0	<0.3 percent	Well contained industrial chemical

Estimates of release rates for a number of chemicals were listed in EPA's study of industrial data on 650 candidate chemicals for testing. For those chemicals for which no release rates were given, an estimate was made on the basis of the dispersive nature of the chemical's uses.

An estimate was also made of the chemical's persistence according to the following table:

Score	Lifetime	Example
3	Infinite (years or greater)	Compounds of metals
2	Order of 1 year	Tetrachloroethylene
1	Order of a few days	SO_2
0	Hours or less	Reactive compounds

The sum of the scores of the two subfactors, release quantity and persistence, was taken as an indication of the environmental burden posed by the chemical.

Factor 3: Occupational Exposure

The source of data on occupational exposure to chemicals was the National Occupational Hazard Survey (NOHS) conducted by NIOSH.

In this survey, approximately 7000 of the most common hazards occurring in the working place were rank ordered. To achieve an occupational exposure score with a range and direction similar to those of the other factors, the Factor 3 score assigned to a chemical was 3.8451 minus the common logarithm of its rank on the NOHS list. (3.8451 is the logarithm of 7000.) Chemicals which did not appear on the NOHS list were given a score of zero, equivalent

Approximately 7000 of the mos. common hazards occurring in the working place were rank ordered.

to having been ranked number 7000 on the survey.

Factor 4: Extent to Which the General Population is Exposed

Four individual subfactors were scored and then summed to measure the general population exposure. The four subfactors were scored as follows:

Subfactor 1: Number of people exposed to the chemical (exclusive of a workplace environment)

Score	No. of people	Example
3	$>20 \times 10^6$	Widely used household products (e.g., wearing apparel, shoe polish, certain surface coatings, common paints and their solvents, common plastics and their additives, detergents, furnishings and carpets, wood cleaning products, refrigerants, natural gas, nonfood packaging materials, flameproofers)
		General air, food and water contaminants
		Automotive products (e.g., gasoline and additives, rubber, surface coatings, plasticizers, flameproofers)
		Products used widely in commercial buildings (mostly same as household, including commercial cleaners, disinfectants)
2	$2\text{-}20 \times 10^6$	Less widely used household products (e.g., uncommon paints, specialty apparel such as baby wear, hobby uses, arts and crafts, tools)
		Regional air and water pollutants, farm chemicals (exclusive of pesticides)
1	$0.2\text{-}2 \times 10^6$	Specialty hobbies (e.g., photography), specialty products
		Neighborhood air and water pollutants from local industries
0	$<2 \times 10^5$	Chemical intermediates rarely found outside the workplace

Subfactor 2: Frequency of Exposure (to the typical person in ranking number of people exposed under Subfactor 1)

Score	Frequency	Examples
3	Daily or more often	General air, food and water contaminants, household products in regular use, material used inside automobiles, clothing
2	Weekly	Hobby crafts, household products used intermittently (e.g., certain cleansers), bleaches, gardening products
1	Monthly	Dry cleaning, certain solvents, house maintenance (e.g., polishes, certain cleaning agents), automobile maintenance
0	Yearly or less frequently	Application of household paints, specialty products

Exposure intensity is intended to reflect the total amount of material that comes into contact with the average or typical person whose exposure has been scored under subfactors 1 and 2.

Subfactor 3: Exposure intensity. This is intended to reflect the total amount of material that comes into contact with the average or typical person whose exposure has been scored under subfactors 1 and 2. Scoring of this factor considered the number of grams of the material that makes contact with the average person in the course of one exposure (daily, weekly, monthly, or yearly as scored in subfactor 2). Thus, for example, a trace pollutant may lead to exposure to a typical person of the order of micrograms per day every day; use of a specialty solvent might lead to exposure of a typical person of the order of grams per day once a year; these would be scored 3,0 and 0,0 respectively on subfactors 2 and 3.

Score	Frequency	Examples
3	High (10^{-1} or more grams per exposure)	Plastics, fabrics, surface coatings, volatile solvents in closed spaces, liquids contacting skin, high concentration gases
2	Medium (10^{-1} to 10^{-2} g per exposure)	Fabric additives, solvents in open spaces or outdoors, dusts, solutes, transitory exposures to vapors or aerosols
1	Low (10^{-3} to 10^{-4} g per exposure)	Low level indoor exposure, volatile substances from home furnishings and building materials (e.g., plasticizers, flameproofers), low volatility solvents, pigments
0	Very low (less than 10^{-5} g per exposure)	Environmental contaminants (low level air, food, and water contaminants), monomers in polymers

Subfactor 4: Penetrability. This is a measure of the material that comes into contact with a person (whether by dermal, inhalation, or ingestion exposure) and that is expected to be absorbed into the body (even transitorily) with potential for interaction with cells.

Score	Penetrability	Examples
3	High (10 to 100% absorption)	Organic solvents in liquid, mist, or aerosol form, vapors and gases if likely to be soluble in body fluids, respirable-sized particles, surface active agents, materials known to have high dermal systemic toxicity
2	Medium (1 to 10% absorption)	Solvents with low volatility and/or larger molecules, organic materials in water solution, waxes and polishes, coarse dusts
1	Low (0.01 to 1% absorption)	Certain solids, dermal exposure to most inorganic materials in water solution
0	Negligible (less than 0.01% absorption)	Polymers, metals

In making the judgements called for in scoring Subfactors 2 and 4 above, knowledge of the chemical's uses was necessary. Use information was collected form the following sources:

1. The Condensed Chemical Dictionary, Ninth Edition, Hawley, Van Nostrand Reinhold Company, New York, 1977.
2. The Merck Index, Ninth Edition, Merck and Company, Inc., Rahway, N.J., 1976.
3. Faith, Keyes, and Clark's Industrial Chemicals, Lowenheim and Moran, Fourth Edition, J. Wiley and sons, Inc., New York, 1975.
4. Chemical Marketing Reporter, Schnell Publishing Company, Inc., New York.
5. Encyclopedia of Chemical Technology, Kirk-Othmer, Inter-Science Publishing Company, New York, 1972.

Ranking chemicals based on production, environmental release and occupational exposure

A linear weighting scheme was used to rank order the chemicals. The rank of the j^{th} chemical, r_j, was computed by the formula:

$$r_j = \sum_{i=1}^{4} W_i \quad \frac{f_{ij}}{i}$$

where w_i is the weight assigned to the i^{th} factor,

f_{ij} is the i^{th} factor score of the j^{th} chemical, and

s_i is a scaling factor chosen to normalize the assigned scores.

The four scaling factors employed were:

s_1 = log 20,850 - 4.33191; 20,850 million lb/yr being the maximum of all Factor 1 chemical production quantities.

s_2 = 6; 6 being the maximum of all Factor 2 environmental release scores.

s = 3.8451 - log 3 = 3.3680; third being the highest NOHS rank among the scored chemicals. (Ranked first and second on the NOHS list were continuous noise and mineral oil, the former not being a chemical hazard and the latter not being among the scored chemicals.)

s_4 = 12; 12 being the maximum of all Factor 4 general population exposure scores.

This choice of s_1, s_2, s_3, s_4, guaranteed that

$$\left| \frac{f_{ij}}{s_i} \right| \leq 1$$

for all i and j, and furthermore, that for each i,

$$\left| \frac{f_{ij}}{s_i} \right| = 1$$ for at least one chemical j.

Appendix B—Biological Scoring

This step of the ITC's procedure extended the scoring of the substances under consideration to statutory factors 5-7 (structural relationships to known toxic substances, available toxicity data, and reliability of test data to predict hazard) of TSCA Section 4(e)(1)(A).

To accomplish this, each substance on the Preliminary List was scored for each of seven biological activity factors by a number of experts. The factors were: carcinogenicity, mutagenicity, teratogenicity, acute toxicity, other toxic effects such as reproductive effects or organ-specific toxicity, bioaccumulation, and ecological effects. After reviewing a summary of information on the biological activity of the substance, each of the experts assigned a score to the substance for the effect(s) for which that expert was responsible.

Each substance on the Preliminary List was scored for each of seven biological activity factors by a number of experts.

At least nine experts were used, with two or three experts separately evaluating each effect. Each expert considered both the summary information and his personal knowledge of the substance and chemically-related substances in assigning scores. Any substantial discrepancies among individual experts were identified, discussed among them, and a consensus reached; in the case of minor discrepancies in the scores for any factor, the scores of the several scores were averaged.

In addition, three of the effects (carcinogenicity, mutagenicity, and ecological effects) were separately scored by government experts from the National Cancer Institute, National Center for Toxicological Research, and Department of Interior, respectively. These scores were averaged with those of other experts.

Three of the effects (carcinogenicity, mutagenicity, and ecological effects) were separately scored by government experts from the National Cancer Institute, National Center for Toxicological Research, and Department of Interior.

Scores assigned for the various effects took the form of a positive or negative numerical score (generally 0, 1, 2, or 3). Assignment of a positive score indicated a judgment that further testing of the substance is not needed for the effect under consideration, while the magnitude of the score indicated the degree to which the effect had been con-

firmed or the dose level at which it had been found. Assignment of a negative score, on the other hand, indicated a judgment that further testing should be conducted, with the magnitude of the score reflecting a judgment as to the level of numerical score that might be anticipated after testing. For example, in scoring a substance for carcinogenicity a score of +3 meant that the substance is well established as a carcinogen in humans or experimental animals, while a score of –3 meant that the substance is strongly suspected of carcinogenic activity but has not been adequately tested. In averaging the scores assigned to a substance by the several scorers for a given factor, no mixing of positive and negative scores was permitted. Any discrepancies between scorers in choosing scores were discussed among the experts and resolved. The criteria applied by the experts in assigning scores for the various factors are described below.

Categories of substances appearing on the Preliminary List were not generally scored as entities, but rather, scores were assigned separately for each of the example substances listed under the category heading in the list.

Biological and environmental scores

A. The five human health effect factors and two environmental effect factors were scored as follows:

Factor 1: Carcinogenicity

a. Positive Scores Assigned:

+3 Established carcinogen in humans or in 2 animal species, or in one animal species in well-replicated experiments

+2 Established carcinogen in 1 animal species

+1 Insufficient or inadequate experimental data for definite conclusions, but either (a) no experimental or structural reason for suspicion, or (b) good negative mutagenicity tests, or (c) low biological activity. (Note: some inert compounds—examples, argon, nitrogen—were given a score of zero on this factor despite not having been tested.)

0 Adequately tested in animals with negative results in each of two species

b. Negative Scores Assigned*:

–3 Needs testing, strongly suspect (close structural relationship to known carcinogen, positive result in validated in vitro test, inconclusive but suspicious positive animal test, etc.)

–2 Needs testing, suspect (structural resemblance to known carcinogen, etc.)

–1 Needs testing, some reason for suspicion (potent organ-specific toxin, enzyme inducer, suspect co-carcinogen, etc.)

* Chemicals presently undergoing testing for carcinogenicity in the framework of the NCI bioassay program were scored as suspect carcinogens. Their special status was documented for the members of the ITC.

c. Criteria for Accepting Positive Test Results (scores 2 or 3)

Validated positive findings in animal studies consisted of any test results which clearly indicated treatment-related carcinogenicity or tumorigenic effects. This was based on the criteria set out in the report of the National Cancer Advisory Board, Subcommittee on Environmental Carcinogenicity, "General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances" (1976).

d. Criteria for Accepting Negative Test Results (including zero scores)

In general, the protocol of the test conformed to, or was reasonably consistent with the current NCI Guidelines (J.M. Sontag et al., Guidelines for Carcinogen Bioassay in Small Rodents, DHEW 76-801). It was recognized that many older tests do not conform to these guidelines. Therefore, good scientific judgment was applied to the evaluation of these tests in order to determine whether differences in protocols significantly weakened confidence in the reported negative results. In assigning a zero score, the guiding principle was the judgment that further testing was unnecessary.

Factor 2: Mutagenicity

a. Positive Scores Assigned:

+2 Mutagen in two or more test systems**

+1 Mutagen in one test system

0 Tested in more than one system with negative results and no reason for suspicion (similar to inactive compounds, etc.)

** These and other scores were normalized to the 0–3 scale for all factors involved.

b. Negative Scores Assigned:

–3 Needs testing, strong reason for suspicion (structural similarity to known mutagen, reported carcinogenicity, teratogenicity, or other cellular toxicity)

–2 Needs testing, some reason for suspicion (structural similarity to known mutagens and/or carcinogens)

–1 Needs testing, no reason to assign high priority

c. Examples of Short-Term Systems Considered for Scoring Were:

The *Salmonella*/microsome test, (Ames), *E. coli* WP2 uvr A, etc. test (Bridges, Witkin), *B. subtilis* M45 Rec-, etc. test (Kada), *E. coli* pol A+/pol A1- test (Rosenkranz), Yeast test (Zimmerman), *Neurospora* test (de Serres) and *Drosophila* test (Vogel). Mammalian cells in culture and in vitro transformations were also considered.

Factor 3: Teratogenicity

a. Positive Scores Assigned:

+3 Confirmed teratogen in humans or in two appropriate animal species

+2 Confirmed teratogen in 1 animal species

+1 Insufficient or inadequate experimental data for definite conclusions, but either (a) no experimental or structural reason for suspicion, or (b) low biological activity

Scientific judgment was applied to the evaluation of these tests in order to determine whether differences in protocols significantly weakened confidence in the reported negative results

0 Adequately tested in two suitable animal species with negative findings for teratogenic activity

b. Negative Scores Assigned:

–3 Needs testing, strongly suspect (close structural relationship to known teratogen, inconclusive but suspicious positive animal tests, etc.)

–2 Needs testing, suspect (equivocal result in animal test, etc.)

–1 Needs testing, some reason for suspicion

c. Criteria for Acceptance of Teratogenicity Tests

Accepted teratogenicity tests conformed reasonably to the recommendations and principles outlined in "Principles for Evaluating Chemicals in the Environment," National Academy of Sciences, pp. 173-182, 1975; and "The Testing of Chemicals for Carcinogenicity, Mutagenicity, Teratogenicity," Department of Health and Welfare, Canada, pp. 137-176, March 1973.

Factor 4: Acute Toxicity

a. Positive Scores Assigned:

+3 extremely toxic: < 50 mg/kg

+2 very toxic: 50-500 mg/kg

+1 moderately toxic: 0.5-5 g /kg

0 very slightly toxic: > 5 g/kg

b. Negative Scores Assigned:

–2 not tested, but suspected to be 50-500 mg/kg

–1 not tested, but suspected to be 500-5000 mg/kg

c. Criteria for Quantitation of Acute Toxicity

Standard systems of toxicity rating based on Probably Lethal Dose in humans were used when available. Lowest Lethal Doses and LD_{50} values in various animal systems were also widely used.

Factor 5: Other Toxic Effects

a. Positive Scores Assigned:

+3 Effects at low doses (<1 mg/kg/day)

+2 Effects at moderate doses (1–10 mg/kg/day)

+1 Effects at high doses (> 10 mg/kg/day)

0 Very low or negligible biological activity (e.g., nitrogen, argon, etc.)

b. Negative Scores Assigned:

–3 Needs testing (structural similarity to another chemical which rates +2 or +3; questionable reports of effects which need confirmation, etc.)

–2 Needs testing, some reasons for suspicion

–1 Needs testing, inadequate information available to give high priority

c. Criteria for Scoring

This factor includes both reversible and irreversible effects, delayed or cumulative toxicity, organ-specific effects, effects on reproduction, behavior, etc. The score entered reflects the toxic effects noted in animals (or in humans if data were available) at the lowest dose-range. If the chemical was reported or suspected to have more than one toxic effect, negative scores for

one type of toxic effect superseded any positive scores for another. In many cases, reports of one type of effect at low doses engendered suspicion of the likelihood of others; in such cases the chemical was scored with the appropriate negative score, unless thoroughly tested.

Factor 6: Bioaccumulation

a. Positive Scores Assigned:

+3 High ($>10^4$)***

+2 Appreciable (10^2 to 10^4)

+1 Low ($<10^2$)

0 Experimental evidence for non-accumulation (<1); water soluble compounds

***The degree of bioaccumulation (more precisely, the tissue-specific storage factor) is defined as the concentration of the chemical in the tissues (at "steady state" or after prolonged exposure) divided by the concentration of the chemical in the ambient medium.

b. Negative Scores Assigned:

−3 Testing important, judged likely to be high

−2 Testing important, judged not likely to be high, but likely to be appreciable

−1 Needs testing, little or no experimental data

c. Criteria for Scoring

Bioaccumulation is used here in its broad sense of the accumulation of a chemical in one or more tissues of an animal (or plant) to levels higher than those in the ambient medium. For purposes of screening chemicals, it was considered significant primarily in cases in which the accumulation in tissues represented an enhanced probability of effects, either on the organ in which the chemical was concentrated, or on animals which feed on the organism which accumulated the chemical. A high degree of bioaccumulation is usually found only in aquatic organisms. For these organisms, bioaccumulation is known to be dependent primarily on water solubility and it is empirically predicted by the octanol/water partition coefficient. Zero scores were assigned to completely water soluble organic chemicals.

Substances which are easily metabolized will not be bioaccumulated even if they have a high partition coefficient (example, chloroform). Thus ease of metabolism was a factor considered in evaluating the potential for bioaccumulation.

Factor 7: Ecological Effects

a. Positive Scores Assigned:

+3 Effects at low concentrations (10^{-9} or less in air or water)****

+2 Effects at moderate concentrations (10^{-7} to 10^{-9} in air or water)

+1 Effects at high concentrations (10^{-6} or greater in air or water)

****In air for gases or vapors: 1 part of chemical per billion parts air by volume (ppb). In water for liquids and solids: 10^{-9} gram per cubic meter (ng/m^3)

b. Negative Scores Assigned:

−2 Testing needed, possibility of major or widespread effects

−1 Testing needed, possibility of minor or local effects

c. Criteria for Scoring:

Ecological effects considered toxic effects on non-human animals and plants, ecosystem effects, effects on atmosphere and climate, ozone depletion, etc. Generally, positive scores (established hazard) were assigned only to a limited number of thoroughly tested chemicals (e.g., pesticides, some metal containing compounds, or some specific chemicals). In other cases, the potential for ecological effects was judged according to availability of data on toxicity in particular, published information on specific tests, structural similarity to compounds of better known ecotoxicity, published data on depletion potential for stratospheric ozone. Zero scores were assigned only to compounds with low biological activity (LD_{50} > 1 g/kg or AQTR > 100 ppm).

Factor 8: Contaminants and Environmental Degradation or Conversion Products

a. Positive Scores Assigned:

+1 Contaminants, etc., known to be important

0 Contaminants, etc., not suspected of being important, or known to be of no importance.

b. Negative Scores Assigned:

−1 Contaminants, etc., suspect, needs testing

c. Criteria for Scoring:

The scores for this factor were not averaged. A negative score took priority over a positive score at any time; if no negative score was assigned to a chemical, the positive score +1 was overriding. A zero score was assigned only if it was scored unanimously by all scorers. The score for this factor was not added: (1) if the principal breakdown product was the major problem and it was the basis for scores on other criteria such as persistence and toxicity (examples: DDE, PAN); (2) for in vivo metabolism of carcinogens to active forms (e.g., arene oxides, activated nitrosamines, etc.).

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EPA's Risk Assessment Guidelines: Overview

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The U.S. Environmental Protection Agency (EPA) risk assessment guidelines for cancer, quantification, and exposure issues are discussed.

The U.S. Environmental Protection Agency (EPA) risk assessment guidelines provide principles, concepts, and standards for evaluating risks to human health from exposure to environmental toxicants. There are separate guidelines for different assessment topics, for example, cancer, reproductive effects, exposure, and mixtures. Each guideline offers information on risk assessment methodology and gives policy guidance on certain difficult or controversial issues.

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Five guidelines were published in 1986. Proposals for new guidelines and proposals to amend some of the 1986 guidance have been published during the last 2 years. This second generation of guidelines not only expands EPA's risk assessment guidance to new subject matter areas, but also introduces new methods and concepts into EPA's formal guidance. Most important, new developments in cancer classification, quantification of risk, and exposure are expected to improve the risk assessment process.

Cancer Classification Issues. A number of classification systems have been invented over the years by various organizations. Some are derived from others. Each has different objectives and results. EPA is considering revision of its own system. EPA has gathered views of scientists outside and inside the agency on what goals such a system should serve, what information it should seek to summarize, and how various kinds of information should weigh in classification. Since classification systems attempt to characterize the likelihood of carcinogenic effects from human exposure, any discussion of classification soon turns to issues where there is lack of scientific consensus. A few of these are human relevancy of animal bioassay results, questions of mechanisms, and the theoretical issue of the intrinsic vs situational hazards of a chemical. These kinds of issues and potential ways of building a classification system to accommodate them are presented.

Quantification Issues. The reference dose (RfD) model, which is derived from the acceptable daily intakes (ADI) approach, has been extensively used by EPA for predicting exposure levels that are likely to be without significant risk of adverse effects for human health effects other than cancer. The RfD can be improved through a critical analysis of its subcomponents, the no-observed-adverse-effect level (NOAEL), and uncertainty factors. Moreover, additional published dose-response methods are gaining favorable review as improve-

New developments in cancer classification, quantification of risk, and exposure are expected to improve the risk assessment process.

ments to the existing RfD, or as enhancements when the regulatory goal is to estimate the likely human exposure. One of these approaches, the benchmark method, is under discussion as an option for quantification.

Exposure Issues. Exposure assessment faces at least three tough issues in the next few years. First, the terminology used by assessors must be standardized. Currently, there are several different schemes used to define exposure and dose, not to mention terms such as reasonable worst case exposure. Second, the potential positive impact of computer technology on data collection, interpretation, and availability is vast, but so are the potential drawbacks of invalidated, ad-hoc computer modeling. How this issue plays out should not be left to chance. Third, the almost universal use of time-weighted average in exposure assessment will face a serious challenge as new toxicological methods such as biological-based dose-response models are developed which need more detailed information than time-weighted average. This may become the largest issue for exposure assessment in the late 1990s.

EPA's Program for Risk Assessment Guidelines: Cancer Classification Issues

Jeanette Wiltse, U.S. Environmental Protection Agency

Issues presented are related to classification of weight of evidence in cancer risk assessments. The focus in this paper is on lines of evidence used in constructing a conclusion about potential human carcinogenicity. The paper also discusses issues that are mistakenly addressed as classification issues but are really part of the risk assessment process.

The Environmental Protection Agency (EPA) has been working toward revising its cancer risk assessment guidelines that were published in 1986. The effort started about 2 years ago; at that time, we were in a "maybe so", "maybe not" mood about it. Given the time and effort it takes, inertia has to be overcome before actually revising the guideline, because in all of these situations, there is a lot of controversy. In 1989 the EPA Risk Assessment Forum sponsored a workshop during which experts from several places were brought together and asked to address several issues about cancer risk assessment. One of these is the subject of my discussion—classification of weight of evidence. Now, that is very arcane. The classification scheme is that small nutshell summary that is the conclusion of a risk assessment on cancer that says do we or don't we think the agent may be carcinogenic to human beings and at what level of confidence we can say so. It's usually a probabilistic statement, "probably yes" or "possibly yes." Sometimes, we know the answer is yes, and that's the end of the statement. The thing that keeps it from being an academic exercise in which scientists sit around trying to see if they can agree on what they would say about an agent, is that as soon as EPA makes a statement, it hits the newspaper. Then my boss has to go on television to explain why it is and what it is because a lot of the industry will get upset when one of the chemicals they market is characterized as being probably, possibly, or known to be carcinogenic to people. Because we use a classification scheme to communicate to risk managers, we communicate the same thing to the public and to industry. It becomes a center of controversy, whether we are ready for it or not. That's why classification schemes are controversial.

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Any discussion of classification schemes is really a discussion of how cancer risk assessment is done, bottom to top. Classification schemes are expressions of a risk assessment that may be several hundred pages long, cover 15 topics, and present lines of evidence from several different scientific disciplines. This paper is limited to the lines of evidence that we use in constructing a con-

Any discussion of classification schemes is really a discussion of how cancer risk assessment is done.

clusion about potential human carcinogenicity—how they're put together—and to identifying some of the major issues that are mistakenly addressed as classification issues but are really just part of the risk assessment process. The elements used in our current guidelines are lines of evidence, or bodies of evidence. Two directly address carcinogenicity: human evidence of carcinogenicity and long-term animal studies of carcinogenicity. The remainder are sources of indirect evidence. None of the sources of indirect evidence answer the question of whether an agent causes a cancer, a tumor, in an animal or a human being. Structure activity doesn't answer the question "Is this carcinogenic?" or "Has this agent caused a tumor anywhere?" Likewise, pharmacokinetics and metabolism can tell you a lot about how the agent is processed in the body, which may be relevant to its potential for carcinogenicity, but it doesn't tell you whether it is or it isn't a carcinogen.

What I will call genome toxicity, a broader term than genetic toxicity, is any kind of an effect on the information a cell contains that helps run its own machinery. Genome toxicity is relevant in considering the potential for carcinogenicity, but it doesn't tell whether the agent is going to cause tumors.

The term I will use for basically everything about toxicity is general toxicity. Is there any other kind of adverse effect that this chemical causes? We use this kind of information to learn more about what happens to the chemical in the body. Does it have a target tissue? Does it have targets in common with those of other agents that we know to be carcinogenic? Does it impact the immune system, for instance, which helps in general with resistance to cancer-causing agents.

Specialized short-term tests constitute another line of evidence. I don't quite know how to describe all of the tests that exist now (that probably didn't exist 5 years ago) that have to do with mechanisms of carcinogenesis. They are not standardized. There are a lot of them, but many of them have to do with manipulating oncogenes and tumor suppressor genes and putting them in systems with agents and seeing what happens; they can tell us quite a lot about mechanisms, if we know how to interpret the results.

All of the schemes and most of the risk assessments for carcinogens have been built on the two direct lines of evidence—on whether an agent is a carcinogen or not. If however, you look at the relevant factors to be included as evidence for carcinogenicity, most of the advances in the experimental sciences are not in those two direct areas. It is the other elements that raise a challenge to classification schemes and risk assessment methods that primarily rely on direct lines of evidence. In my opinion, all of the indirect lines have become increasingly useable and powerful in predicting risk or in putting together a story of the structure of the chemical: how it is likely to behave in a biological system, and the likelihood of its carcinogenicity. In the future, I think the long-hoped-for substitutes for long-term animal bioassays, which take so long and cost so

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much, will arise out of these other lines of evidence. The challenge to our classification system at EPA comes, in part, from that. It is very heavily reliant, as are our other systems, on direct evidence of carcinogenicity. That is still appropriate. We are not yet at the stage of being able to walk around that. The question is whether any system, EPA's included, allows enough space for growth for the remaining kinds of information and for their power to tell about the potential carcinogenicity of an agent.

Some existing classification schemes include EPA's in 1986, the International Agency for Research on Cancer (IARC) revision to its 1987 scheme, and something called the Tripartite scheme, which, I think, was published by Canadian, U.S., and European scientists. I believe that the European communities use it for guidance. A paper that is to be published soon by the American Industrial Health Council (AIHC) that creates still another kind of classification system addresses the question, How do you deal with questions of animal bioassay data that may not be relevant to predicting human carcinogenicity for one reason or another?

Table 1 shows one classification scheme. These are the "boxes" into which the predications and the risk assessments are sorted. Behind each of these is a complete risk assessment. Obviously, this is a terrible way to portray any kind of scientific risk assessment because it boils it all down to one or two words. Nevertheless, the public and our risk managers need to know what we

Table 1. EPA Cancer Classification Scheme: Weight of evidence based on human and animal evidence

Human evidence	Animal Evidence				
	Sufficient	Limited	Inadequate	No data	No evidence
Sufficient	A	A	A	A	A
Limited	B1	B1	B1	B1	B1
Inadequate	B2	C	D	D	D
No data	B2	C	D	D	E
No evidence	B2	C	D	D	E

There may be instances in the classification of both human and animal data indicating that different categorizations than those given in the table should be assigned. Assignments are tentative and may be modified by ancillary evidence. All relevant information is evaluated to determine if the designation of the over-all weight of evidence needs to be modified. Relevant factors to be included along with the tumor data from human and animal studies include structure-activity relationships, short-term test findings, results of appropriate physiological, biochemical, and toxicological observations, and comparative metabolism and kinetic studies. The nature of these findings may cause an adjustment of the overall categorization of the weight of evidence.

A = HUMAN CARCINOGEN

B1 = PROBABLE HUMAN CARCINOGEN
Limited evidence in human studies

B2 = PROBABLE HUMAN CARCINOGEN
Sufficient evidence from animal studies, inadequate evidence or no data from human studies

C = POSSIBLE HUMAN CARCINOGEN

D = NOT CLASSIFIABLE AS TO HUMAN CARCINOGENICITY

E = NO EVIDENCE

Fig. 1. EPA carcinogenicity classification scheme.

really think of the potential of an agent to cause these effects. So, in one way or another we are going to be boiling it down for that purpose.

What is hoped is that a classification scheme will allow us to be consistent in the way we boil it down from one data set to the next. If it is kept simple, people will be able to understand it. Figure 1 shows the EPA cancer categories. All the way from "known" to be a human carcinogen down to "not carcinogenic." The IARC classification system, Fig. 2 is very similar. As a matter of fact, our EPA system derives from the IARC system. But the IARC has often relied on the two direct lines of evidence, the human data and the animal data (long-term animal studies). They don't really have a place in their scheme for using all other hazard elements. They wouldn't use structure-activity, I don't think. They are beginning to look at other things, but so far their scheme is not designed to fully accommodate lines of indirect evidence. So, although these look very similar, EPA has tried to use more of the indirect evidence in its decisions than the IARC has.

One of the criticisms of weighting schemes is that in EPA's work (and possibly IARC's, although I'm not sure), one line of evidence can drive the decision. For instance, a couple of positive animal bioassays and you're already way up the scale. Other kinds of data won't have much impact on this even if other lines of evidence make it extremely doubtful that those two animal bioassays can be relevant to humans. In such cases you have to undo the initial classification—sort of climb down out of it. That's the criticism—that the initial decision about how to rank the chemical is more driven by one side of the evidence than it is the other side of evidence. A true weight of evidence scheme would not work that way. It is a characteristic of the schemes up to now that they have put overriding weight on the direct evidence. I'm not criticizing that — we have to do that. What I'm saying is that this approach tends to muscle out the potential growth and strength of some of the other data.

A	=	CARCINOGENIC TO HUMANS
2A	=	PROBABLY CARCINOGENIC TO HUMANS Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals
2B	=	PROBABLY CARCINOGENIC TO HUMANS Limited evidence of carcinogenicity in humans in the absence of sufficient evidence in experimental animals. Also when there is inadequate or non-existent evidence of carcinogenicity in humans but sufficient evidence in experimental animals.
3	=	NOT CLASSIFIABLE AS TO CARCINOGENICITY IN HUMANS
4	=	PROBABLY NOT CARCINOGENIC TO HUMANS

Fig. 2. IARC carcinogenicity classification scheme.

What is hoped is that a classification scheme will allow us to be consistent in the way we boil risk assessment down from one data set to the next.

Finally, another criticism—that people tend to pigeon-hole data sets by the numbers. The use of numerical schemes tends to promote routine activity—we don't think about how we do things or analyze them as well as we should. For these reasons we might consider changing our classification and weight of evidence schemes. The experimental database around which things

People tend to pigeon-hole data sets by the numbers.

were originally designed has changed drastically. To accommodate this change, we may need to be more explicit about using newer research data in our classification schemes. We don't actually make it impossible to use that data now, but we could be more explicit about how those data are weighed with direct data to arrive at conclusions. One criticism is that we don't classify potential carcinogenicity of an agent differently by route of exposure. If it's known to be a human carcinogen by the oral route it is tagged as a known human carcinogen. We don't emphasize the fact that data may also show that by the dermal route it's really not expected to be a carcinogen hazard. In the future we might be able to say that it is a known human carcinogen by the oral route and something else by the dermal route.

Over the last few years one of the biggest controversies dealing with cancer risk assessment has to do with questioning the relevance of animal carcinogen bioassays to human carcinogenesis. This issue increasingly confronts anybody dealing with long-term animal bioassays. There are certain tumor types that instantly cause people to say "Oh that's not relevant in considering human carcinogens." I don't think current schemes deal with this issue particularly well and I don't know whether they need to. One reason we find it hard to deal with some of these questions is that some of the issues go back to indirect evidence and the possibility of weighing the evidence differently. That's why I am not sure that relevance deserves special treatment. Nevertheless it is something that causes people to question the current scheme.

Among people in EPA who are looking at revising the guidelines, a lot of discussion has to do with the relevance of animal data. How do you discuss things like that? Where do you make a place in your classification scheme to show how you weighed that kind of issue? How do we accommodate this fact to make classification schemes accommodate what I think is going to be an exploding database of mechanisms research in the next 10 or 15 years? I think we are going to be doing research in the future for strictly mechanistic information.

The numbers and letters of classification schemes are a problem. This is a personal question for me; I look down all these lists of alphanumeric schemes for classifying and I get lost. I can't translate between systems. Numbers and letters are beginning to get to me a little bit. I hope we can find a way to use words for these classifications. The question of classifying by route of exposure is under discussion, so that's a possibility. Another issue is whether the potency of a carcinogen should be part of the weight of evidence. That is, when we say it's a probable human carcinogen, is it at a high dose or at a low dose? Is it somewhere in the middle? The question has been raised about whether those kinds of issues belong in weight of evidence for the classification schemes.

In answering these questions (these are more my statements than EPA's), I think we will have to provide more explicit rules

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and a greater weight for indirect evidence aside from human studies and animal bioassays. The time has come to start classifying by route of exposure.

I sat down and tried to picture a matrix that would bring potency into discussions of whether something is a potential carcinogen, given the trouble we have figuring out what the potency is. I couldn't figure out how to do that without bogging down. Some people are trying to push for a view that something like a promoter that may have some kind of threshold is not really a carcinogen. It is set aside in a category by itself. A lot of people tend to think that carcinogens are strictly agents that are genotoxic and that those are the ones that should be classified, not promoters. I don't now expect the agency to categorize differently according to mechanisms that may be at work. The means by which something causes or might cause cancer is not necessarily part of the classification. It certainly would be a limitation, a part of the hazard characterization, but not necessarily a part of whether saying something is or is not potentially carcinogenic.

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We may be able to propose something next year; I hope we can. We have not really come to closure even within our work groups about how to deal with many of the issues. We are in the midst of a sea of data that didn't exist when the very first guidelines came out. A lot of the data around now—mechanisms is an example—weren't there; now we are afloat in it. We will get out the new guidelines if it's at all possible, but we probably won't finish until next year.

EPA's Program for Risk Assessment Guidelines: Quantification Issues

Michael L. Dourson, U.S. Environmental Protection Agency

The quantitative procedures associated with noncancer risk assessment include reference dose (RfD), benchmark dose, and severity modeling. The RfD, which is part of the EPA risk assessment guidelines, is an estimate of a level that is likely to be without any health risk to sensitive individuals. The RfD requires two major judgments: the first is choice of a critical effect(s) and its No Observed Adverse Effect Level (NOAEL); the second judgment is choice of an uncertainty factor. This paper discusses major assumptions and limitations of the RfD model.

Work on the noncancer quantitative guidelines started in 1984. After a year of inconclusive discussion, the technical panel disbanded and was replaced by an Acceptable Daily Intake (ADI) work group. The point was to get colleagues together from various agency offices to look at noncancer assessments prepared by the individual offices. After two years of ADI work group experience, the agency restarted its guideline development for noncancer.

This paper will discuss some of the quantitative procedures associated with noncancer risk assessment. The first is reference dose (RfD). Two other quantitative procedures exist that are quite new. One is referred to as a benchmark dose and the second is loosely classified as severity modeling. A fourth procedure exists called decision analytic approach, which the Office of Air Radiation uses with it's air pollutants, but this will not be discussed here.

An RfD is an estimate of a level that is likely to be without any health risk to sensitive individuals. Some think of an RfD as being below a threshold dose. This, however, is not necessarily universally accepted.

The RfD requires two major judgments, the first of which after looking at all the data is to choose a critical effect(s) and its No Observed Adverse Effect Level (NOAEL). The second judgment is the choice of an uncertainty factor after looking at the entire data base and determining the status of missing data.

Estimating RfD requires choosing a critical effect(s) and its NOAEL. It also requires choosing a composite uncertainty factor.

The first assumption of the RfD model is that a threshold exists for toxic effects. Obviously, for some chemicals thresholds are thought not to exist. Where a threshold does not exist for a toxic endpoint, calculating an RfD is not appropriate. We also assume that the RfD represents a subthreshold dose and that if we protect against a critical effect, we protect against all adverse effects. A major limitation is that although the choice of the NOAEL for the critical effect uses all of the data, in the RfD model only the NOAEL dose is used quantitatively. Also, if we use only a particular NOAEL, we are losing information in the

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study on which you have chosen to focus. Another limitation is that uncertainty factors are imprecise and the RfD model cannot estimate risks above the RfD.

Regarding the quantitative issues of the RfD, we have focused during the last couple of years on the statistical variability of a NOAEL. A paper was published by Brown and Erdreich in 1988 discussing this effort. The authors did not focus just on the value of a NOAEL but also considered its limitations or variability. It is thought that if NOAELs are based on larger numbers of animals per dose group, the NOAELs will tend to decrease because by looking at more animals an effect is more likely to be apparent. Such latter NOAELs are likely to have a tighter variability.

Another aspect to this area of research is looking at data that fall behind various uncertainty factors. A publication by Hattis, Erdreich, and Ballew (1987) focused on the uncertainty factor for within-human variability. It characterized the statistical distribution of the uncertainty factor on the basis of human pharmacokenetic modeling or human pharmacogenetic parameters. The authors showed that for healthy individuals, an uncertainty factor of 10 covered about 96% of the variability. This supports the notion that tenfold uncertainty factors are conservative and that values less than 10 are actually more likely to occur. Other published work yields similar distributions. For example, EPA often uses a tenfold uncertainty factor to extrapolate from a subchronic to a chronic exposure, as do other federal agencies. This factor accounts for about 96% of the comparisons of subchronic to chronic extrapolation; the average factor is about 2 or 3. One area of our research is focused on trying to get a better quantification of NOAELs, uncertainty, and modifying factors, with the end result of trying to characterize the probability distribution of a reference dose.

Our research is focused on trying to get a better quantification of NOAELs, uncertainty factors, and modifying factors, with the end result of trying to characterize the probability distribution of a reference dose.

Another area of research is the benchmark dose. Several investigators are looking at this and a number of papers have been published. The first was by Crump (1984), followed by Dourson et al., (1985). The idea behind benchmark dose is to use all of the data on a particular end point. A mathematical model is applied to that data and then an estimate is made of upper confidence limits, perhaps 95%. Depending upon how many animals were used per dose level and how good the data fit along the slope, one might get tight 95% confidence limits or you might get confidence limits that were less tight. The idea of a benchmark dose, then, is to focus on a particular point along this curve. In the 1984 and 1985 publications, 10% was used, but only as an example. The lower 95% confidence limit on the dose associated with a 10% response level would be the benchmark dose, and for the rest of the toxicity database one uses different uncertainty factors. Reasons for different uncertainty factors might include disparate severity of effects and slopes of dose-response curves. Again, the benchmark dose is one way of using more of the information to get a reference dose. Other issues regarding the benchmark dose

The idea behind benchmark dose is to use all of the data on a particular end point. A mathematical model is applied to that data and then an estimate is made of upper confidence limits, perhaps 95%.

approach include deciding which end point to choose as the benchmark. Several published examples used 10%, but 1%, 5%, or other values could be chosen. With these various benchmarks, which type of uncertainty factor should be applied? Several statistical issues exist as well, but these will not be discussed.

Another idea is to plot what is called the severity of the toxic effect. Even before the idea of severity of toxic effect can be broached, there are a host of issues associated with adversity and severity of effect that are not well worked out even within the Agency. For a particular organ system, it might be very easy to say some effects are clearly not adverse and that some effects are clearly adverse. For example, an increase in smooth endoplasmatic reticulum in the liver, clearly caused by the chemical, may not be an adverse effect. In fact, it might be protective; whereas infiltration of liver cells with fat is clearly a sign of disfunctioning liver cells and is considered adverse. However, for developmental toxicity the question of what is adverse may not be as clearly defined. In some areas, such as immunotoxicology, what constitutes an adverse effect is only now being discussed. Let us assume for the moment that we have a good handle on the differences. Then, for any particular chemical it is possible to plot the probability of a No Observed Effect Level, the probability of a NOAEL, and the probability of other categories of toxicity with increasing dose.

One can then take several dose scales for different chemicals, normalize them, and compare the various risks of different chemicals above the RfD based on plotting the severity data for each individual chemical. On the basis of this analysis, the risk manager might choose to regulate chemical B differently than chemical C if they were both over the RfD by a tenfold factor. As with benchmark dose, many issues also exist with severity modeling. For example, what constitutes an adverse effect? What does the severity of effect mean? The mathematical model currently used is just one of many that could be used, and there is a discontinuity in the curve that hasn't been solved yet.

In summary, EPA uses reference doses for noncancer risk assessment. This method is part of our developing risk assessment guidelines. In addition to the RfD, other quantitative approaches exist such as the benchmark dose, and the severity of toxic effect. More publications on these quantitative procedures may find their way into the literature in the near future.

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EPA's Program for Risk Assessment Guidelines: Exposure Issues

Michael A. Callahan, U.S. Environmental Protection Agency

Three major issues to be dealt with over the next ten years in the exposure assessment field are: consistency in terminology, the impact of computer technology on the choice of data and modeling, and conceptual issues such as the use of time-weighted averages.

The first exposure assessment issue, terminology, needs to be dealt with immediately. The definition of exposure itself has been controversial. There is general agreement that exposure to a chemical substance means contact of that substance with a person or other organism, and that exposure assessment is the qualitative or quantitative description of that contact: intensity, duration, frequency, and route. Other aspects of the terminology, however, are not standardized. These include differences in how the terms 'exposure' and 'dose' are used, units for each, and differentiation of different types of dose: for example administered dose, applied dose, and absorbed dose. the U.S. Environmental Protection Agency (EPA) expects that its *Guidelines for Exposure Assessment* [57 FR 22888], which includes a glossary of terms, should be the major vehicle in assuring consistency in terminology both within the Agency and with the outside scientific community.

The second issue which must be dealt with in the next few years, is the potential impact of computer technology on data collection, interpretation and availability. The technology exists to put enormous data storage and retrieval capabilities in the hands of assessors through personal computers with CD-ROMs. EPA has begun investigations of the usefulness of a risk assessment library on CD-ROM [EPA/600/9-91/045a] and a collection of models with their documentation on CD-ROM [EPA/600/C-92/002]. These have enormous potential for positive impact on the exposure assessment field. However, without validation of models, the availability of large amounts of data and models might raise the question of validity of the assessments, which would be a negative impact on the field. We are at a crossroads today and it is up to the exposure assessment community to make a wise choice of paths.

The third issue which must be dealt with in the next three to ten years, has to do with the basic way in which carcinogen exposure assessments are done. The almost universal use of time-weighted averages for these types of assessments will face a serious challenge as new toxicological models such as biologically-based dose-response models are developed. These

Aspects of terminology, however, are not standardized. These include differences in how the terms 'exposure' and 'dose' are used, units for each, and differentiation of different types of dose:

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new models will require more detail from the exposure assessment than just a time-weighted average exposure or dose. In some cases, a detailed time-intensity profile will be required as input to the dose-response model. This is a challenge for the exposure assessment community that must be addressed and met soon. Only then will we be ready for the types of risk assessments we can expect in the latter part of the 1990s.

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Information Applications: Rapporteur Summary

Sidney Siegel, National Library of Medicine

An increased level of mathematical sophistication will be needed in the future to be able to handle the spectrum of information as it comes from a broad array of biological systems and other sources. Classification will be an increasingly complex and difficult issue. Several projects that are discussed are being developed by the U.S. Department of Health and Human Services (DHHS), including a directory of risk assessment projects and a directory of exposure information resources.

As rapporteur to this group, I will quickly identify what I believe has been said and what was not said. Also, I may comment on what could be. Through discussions, we can hopefully generate within the symposium participants a sense of *quo vadis*: where are we going and why? Efforts to put this symposium together were obviously very intense. I have put conferences together myself, and it can be described as pure aggravation. Throughout the discussions, I had the impression that many presentations could be characterized as preaching to the converted. I think many of the folks here don't have to be converted or need to have identified again what the problems are that we face; we need now to say which way we are going. We need to address issues relevant not only to which way we should go but also why.

Session A covered chemicals, health effects, and information needs. The titles were *The Problem of Living in a World Contaminated With Chemicals, Environmental Laws Regulating Chemicals, Information Needs for Risk Assessment, and Information Needs for Risk Management Communication*—all not only interesting but very difficult and ill-defined subject areas. The history and development of an awareness of the impact of chemical agents on humans and on the other compartments of the environment were outlined. Laws relevant to this symposium were identified. However, we should be sensitive to the fact that there are at least 18 major pieces of federal legislation that impact the development, production, distribution, use, and eventual disposal of chemical agents. This listing does not include laws that have been promulgated by the 50 states. This session also addressed some of the complexities associated with identifying and utilizing data and information that could be supportive of the assessment and management of risk. Problems associated with coordinating risk management across federal and/or state agency lines, especially when Superfund sites are involved, were discussed. These problems are not trivial.

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Session B, Toxicology Information Resources, Challenges, and Needs, described the evolution of systems and reminded me some of discussions on the theory of chaos. It is also apparent that Session B chaos can be ordered through the appropriate

and imaginative application of computer-based technology.

Session C dealt with the application of toxicology information in establishing priorities, chemical testing, hazard ranking, and risk assessment. In this regard, Structure Activity Relationships (SAR) was addressed as one of means to assess issues relevant to new chemical substances under TSCA, as was the use of Quantitative Genetic Activity Graphical Profiles (GAP) for Use in Chemical Evaluations. The Interagency Testing Committee Chemical Nomination and Selection Process was discussed. (During my time at the National Cancer Institute [NCI] I had $250,000 to support activities relevant to QSAR, but I couldn't get other branch chiefs involved because they felt QSAR was too close to the practice of witchcraft.)

We heard a discussion of the GAP information profiles that identify the start of accumulating the intelligence base that will be a new means to help us understand the relationships in and among a broad spectrum of different kinds of data. I think this is going to be one of the more interesting and intriguing areas of the future. An increased level of mathematical sophistication will be needed to handle information derived from a broad array of biological systems and other sources. We have just started to address the potential of those kinds of multidimensional information processing resources.

In Session D, Guidelines Used to Assess Toxicological Hazards, the titles included were *Overview of the EPA Programs for Risk Assessment Guideline Development, Cancer Classification Issues, Quantification Issues, and Exposure Issues.* Scientific issues were discussed that in and of themselves are difficult; these issues are further confounded by the fact that they are required to be precisely defined in order to be implemented under law. Such definitions will require involvement of all our communities and interested citizens including the federal and state organizations responsible for their application. Especially highlighted during this session was a concept that goes back beyond Linnaeus to the time when we had witchdoctors and shamans guiding us through our daily lives. That is the concept of the classification of toxic substances. These witchdoctors and shamans were able indeed to roughly sort out some of the classifications of substances that they dealt with. This was done by setting up captured prisoners of war into three groups—one group got the unknown substance, a second group a known agent, the third group nothing. So, they quickly could do LD_{50}s concerning the substances, and the shamans could further build their own treatise on poisons useful for management. Thus, classification has been around for some time. Classification is not a trivial issue because once you put a tag on something, you are stuck with it, especially if you are part of a regulatory function of government. By misclassification you may hang yourself as well as other federal and state agencies out to dry. Of course, in addition, there are significant impacts on private-sector organizations that must respond under law to such classifications.

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Some of the things coming in the near future are projects, that I think will be useful to all the organizations represented here. First, in the DHHS we are trying to put together a Directory of Risk Assessment Projects. Risk assessment activities are costly projects and people need to be aware of what has been paid for with public funds. I thought when I got the money for the effort it was going to be a technical piece of cake; technically, it is a piece of cake. Then we ran into the political issues — trying to get the heads of the various DHHS agencies to identify the risk assessment projects in their organizations. Things are moving forward, however. We have had excellent cooperation from one of our organizations in DHHS, the National Center of Toxicologic Research (NCTR) represented at this meeting by Angelo Turturro. It has been possible to work together to sort out which of their projects would be relevant for such a directory.

Another activity, which in its own way is going to be politically even more difficult, has gotten support from the Interagency Task Force on Cancer, Heart, and Lung disease. It is a directory of exposure information resources developed across the federal establishment; we hope to extend it to include state environmental and health agencies. So far, a 20-page questionnaire is now being tested by a limited number of organizations. Of all the information needs concerning risk assessment and management and the effects of chemical agents on humans and other compartments of the environment, the greatest need is for information on exposure that is scientifically timely, complete, and credible.

Yesterday, we heard about the many prioritization schemes out there. Federal agencies have put together between 36 and 40 major prioritization schemes over the years, of which I have been involved in about half. These are variations on a basic theme—What is the substance, how much is produced, and where and how is it distributed and used? Details of such schemes are driven by the needs of the particular organization compiling it. We need much more sophistication in the various models that are used to support the assessment and management of risk. The sophistication or applicability of models needs to be increased. In communicating with users and affected communities, we need to explain the capabilities and limitations of a particular model.

This symposium understandably focused only on chemical agents. However, humans and other compartments of the environment are also concomitantly exposed to biological and physical agents, making the overall picture of exposure even more interesting and complex. Looking at only one dimension of exposure is naive and will not serve us well.

To address exposure overall will require a significant effort in communication and coordination among federal and state agencies and into the private sector. The problems we face in this effort can be best described as nontrivial, and solutions will require the best input we can get.

Finally, I leave you with a quote that was translated into Latin by

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the daughter of one of the people in my office who is quite a scholar. It's a takeoff on Rene' Descartes and simply says "If I think a system, it can be built." As you see what your needs are, imagination should be the least limiting factor in determining how to efficiently and effectively meet them. "Si Rationem Puto, Potest, Achficari!"

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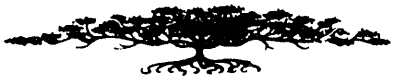

How Information Resources are Used by Federal Agencies in Risk Assessment Applications

William E. Legg, U.S. Army Environmental Hygiene Agency

This paper discusses the structure and responsibilities of the U.S. Army Toxic and Hazardous Materials Agency.

In the mid-1970s an agency was established within the Department of Defense, known as the U.S. Army Toxic and Hazardous Materials Agency (USATHAMA). The primary reason for starting this organization was the Rocky Mountain Arsenal in Denver, Colorado. Those of you familiar with Rocky Mountain Arsenal know that there are about 165 functional hazardous waste sites at the arsenal. They are contaminated with such things as diisopropylmethyl phosphinate, other chemicals associated with the production of nerve and blistering chemical warfare agents, and several general-category industrial chemicals. Since the inception of USATHAMA, the number of problem installations has risen, and thus, Rocky Mountain Arsenal is no longer our sole problem. For example, 34 Army installations have been identified with 36 functional sites that are either on the National Priority List (Superfund) or are proposed for Superfund listing. In Resource Conservation and Recovery Act (RCRA) facility investigations alone, there are some 3500 installations that deal with roughly 5000 functional sites. It's a target-rich environment for any risk assessor. Approximately 18 months ago, the Surgeon General of the Army recognized the need for medical review of the health risk assessments. Inherent in this review process is the tenet that the Surgeon General of the Army is responsible for the health and well-being of all military and civilian personnel working on Army installations. Further, the Surgeon General has assigned the U.S. Army Environmental Hygiene Agency (USAEHA) the task of serving as his executing agent for review and performance of health risk assessments. Therefore, Program 39, of which I am the chief, was created.

Thirty-four Army installations have been identified with 36 functional sites that are either on the National Priority List (Superfund) or are proposed for Superfund listing.

At USAEHA, we have what I refer to as the "olive drab" version of the Environmental Protection Agency (EPA). We continuously interact with EPA headquarters. Currently, we are assisting Mr. Chet Osmond from the Office of Solid Waste in conducting energetic compound technology transfer information seminars throughout the United States. The military has several sites that perform open burning/open detonation of explosives and propellants in above-ground and below-ground disposal operations. Many things can go wrong in these operations, and we are trying to assist the permit writers in determining

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the associated environmental and health concerns.

I have 8 individuals, including myself, executing the health risk assessment mission. I have approval to fill 32 positions to accomplish the mission.

Our agency has a matrix structure. We are staffed in directorates and divisions that incorporate the disciplines of toxicology, air pollution engineering, surface-water and groundwater sciences, health physics, laser and microwave technology, entomology, occupational and environmental medicine, and so on. I draw from the expertise in these directorates/ divisions to form the risk assessment review or on-site risk assessment teams.

What problems do I see in this arena? For reasons similar to those already discussed this morning, there is a need to consolidate and integrate the numerous databases for ease of use. The 30 or 40 databases available are extremely difficult to use because of differences in the programming language/hierarchal structure of the programs. Similarly, some commonality of use of program type is needed across the board, not only from the user and contractor's perspective, but also from the EPA regional perspective.

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Finally, I believe that we are not adversaries in this endeavor; we must be partners. The result should be a clean environment that is protective to human health. We must accomplish our tasks as partners, not as adversaries.

Tactical Approach to Maneuvering Within the Chemical Contamination Labyrinth

Timothy W. Joseph, Department of Energy

The Department of Energy (DOE) recognized the need and accepts the responsibility for understanding the reality and mitigating the consequence of the complex chemical contamination legacy it inherited as well as controlling, reducing, and eliminating extant emissions and effluents. The key to maneuvering through this complicated and multifaceted labyrinth of concerns, from which a meaningful, high quality, and cost-effective restoration/mitigation machine is then set in motion, is the ability to perform accurate, factual, and explicit health and environmental/ecological risk assessments. Likewise, the common denominator for carrying out this essential task is to have access to comprehensive and reliable data of known quality with which to perform those analyses. DOE is committed to identify the data universe; to technically scrutinize and ensure the quality of that data; to develop efficient and cost-effective means to maximize the handling, utilization, and sharing of that universe; and to undertake those assessments. DOE views this as an effort that can only be accomplished through a merging of the technical excellence that exists within federal and state agencies, academia, and industry. The task at hand is so large that only by integrating that intelligence base can we hope to accomplish the goals of establishing meaningful standards, developing functional and effective solutions, and providing quality guidance at a national scale.

No matter how good our models are, no matter how applicable the assessment techniques are, and no matter how proficient the experts are in dealing with these problems, the ability to perform environmental, ecological, and human health risk assessments relies entirely on the universe of data. It is perhaps the most perplexing and complicated part of our assessment. Models can be adjusted and verified, techniques can be improved, and more can be learned. However, we cannot merely acquire all the data we need.

Historical data, that abyss we find ourselves so often trying to analyze, is finite; it's all we have. We must deal with its integrity and its relevance. We must know how to best utilize the historical data that we have. New data, especially chemical data, is very costly to collect and analyze. Laboratory toxicological data and environmental and ecological effects data can make the chemical data cost look cheap in comparison. It is the access and use of that data universe that we rely on to carry out our analysis.

In performing assessments, we start with historical data. We look at all past operational data that we can find, such as what the facilities did, how long they were in use, what materials were used or must have been used, and any operating parameters/specifics we can determine. We look at operational history and any records we can find, such as old manifest or disposal records; we talk to past employees. We then try to correlate what hard information we find with what we believe should have been taking place in that facility if they were doing what we know or believe they were supposed to. We then attempt to determine actual disposal methods or what logic tells us would have been their disposal methods at the time. We look closely at the environmental setting, old photos,

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old maps, how the area has changed since that time, what areas were used for disposal, and what areas would probably have been used for disposal. We look at the natural setting, the soils, the geochemistry, the geology and hydrology—subsurface and surface. We look at climatic and meteorological data to address transport and fate. It is imperative that we fully understand the transport and fate mechanisms for the facilities that have been operating for more then 45 years.

We then determine the contaminants on which we will concentrate. Critical, of course, is the quality of the data. Are they valid? How were they collected? If data exist on volatiles, were samples collected in a bucket and then dumped in a sampling jar? If so, those data are useless. We look at the analytical aspects — did the sample preparation introduce contaminants? How accurate and precise was the instrumentation *vs* the detection limit? Was the detection limit influenced by moisture content? We need to understand the multitude of aspects associated with the quality of the data, which is sometimes very difficult to determine and more often than not, cannot be determined.

Next, we establish a list of tentatively identified compounds. We look at it, and compare it with our knowledge of the facility. We then may be forced to go back because things don't correlate.

We attempt to determine background. It is preferable, however, to use the word "reference" rather than "background." "Background" is an uncertain criterion. Is it 100, 150, or 500 years ago, or is it some number of years BC? Unless we can beam up to the Starship Enterprise and use its sophisticated sensors, we don't know what background is or should be. Where do we see the compound or chemical? Where would we expect to see it naturally and at what levels? We have experienced 150 years of industrialization with an extreme variety of effluent and emissions; we have more lead in our environment, as identified to us yesterday, from our automobiles than from industry. From agriculture we have complex of insecticides, herbicides, etc. How do they change? What about synergy? How long have they been there? This complicates determination of background. Background implies "before man's influence, completely natural," whereas reference suggests "normal, expected, prior to any influence from the subject facility."

We then try to correlate the contaminants and concentrations with locations, factor what we believe the "reference" concentrations should be, sample selected environmental and ecological parameters and organisms, and perform selected toxicity studies when warranted. We also use biological sampling in an attempt to back-calculate environmental contaminant levels. This is an extensive, very complicated, and expensive procedure. Without reliable data of known quality, we are significantly restricted in what we can do. With good data, we can determine or reconstruct sources and doses.

Having what we consider to be good data, we must then be able to accurately determine the

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actual risks and project with some precision the potential risks. How we do that is important. The best minds in government, industry, and academia are working on just that. New quality guidance from Environmental Protection Agency (EPA) and the universities is available and growing. Recent documents from EPA are quite impressive. It is a complicated yet very exciting field. With our severely limited budgets, greater scrutiny from congress, and the public, we can only keep our heads above water and progress toward solutions to these complex and very "expensive" problems by combining our respective intelligence to achieve solutions. The best tactical maneuver we can make is to join forces, combine that intelligence base, and become an efficient and effective technical team. Together, we can become both the model of technical excellence, as well as the model for approaching and accomplishing quality, verifiable, and reiteratable risk analysis.

One positive consequence of the pressures placed on our agencies as a result of these limited budgets is that it has brought us together as partners in solving these problems, in contrast to working in our own respective closets, emerging once in a while to merely state positions or make criticisms. The cooperation between our agencies, the states, industry, and academia, has been outstanding. The number of guidance documents generated, technical publications developed and written through joint reviews, planning efforts made, and the close technical collaboration achieved between us, has produced a genuine technical and professional regard and fellowship.

This complex and enigmatic national concern—health and environmental risks of chemical exposure—requires an even greater team effort. Again, the best tactical measure we can take is to combine that joint intelligence. In a very real sense, we simply can't solve the problems by ourselves or merely wish them away. DOE is steadfastly committed to do all it can toward assessing the problems and reaching solutions. It will continue to provide the most accurate and complete data base possible and engage the best scientists to do the best research to achieve this goal.

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Information Resource Use and Need In Risk Assessment

Angelo Turturro, U.S. Food and Drug Administration

The manner in which the Food and Drug Administration (FDA) uses information resources comprises an interesting illustration of federal agency information use. A description of the context in which risk assessment occurs within FDA is followed by a discussion of information access and use, as well as a practical example.

FDA has six Centers, three of which address regulation of drugs, biologics (e.g. vaccines) and devices (e.g., pacemakers), and radiation health. The evaluation of risk of drugs and biologics is a process incorporating judgement and involving risk comparison. The agents are being considered because they solve some therapeutic problem; judgement of their safety and efficacy must weigh in as considerations the results of not using them as well as the existence of alternatives.

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These factors with the addition of engineering considerations are also important to making evaluations about medical devices. Not only does the chronic toxicity of a device, such as an artificial heart have to be considered, as does its capability to do the job, there also has to be a judicious evaluation of factors such as the possible failure of the device. In many ways the requirements for an assessment for a device are more similar to the kind of assessment being done by the Nuclear Regulatory Commission for possibilities of a nuclear plant failure than to the kind of assessments an agency like the U.S. Environmental Protection Agency (EPA) does on agents. Thus, these responsibilities are performed by using a risk assessment methodology that is oriented toward their risk-balancing procedures.

Risk assessment stresses other considerations in the remaining three FDA Centers. Risk assessment in the Center that deals with veterinary drugs is most often directed at the risks associated with the residues of drugs given to animals when they are used for food. When considering this specialized area, the efforts are similar to those conducted by the Center that addresses the safety of the food supply, which, oddly enough, also evaluates the risks of cosmetics. Risk assessments similar to these are performed at the National Center for Toxicological Research, which also conducts research into general questions related to risk assessment.

Risk assessment is part of risk management.

These differences emphasize the point that risk assessment is part of risk management (Turturro and Hart 1987). Nobody does a risk assessment unless it is for a regulatory reason, and the reason for the assessment impacts on the assessment itself. If the purpose of an assessment is to weigh

alternatives for a necessary procedure, it will be conducted differently than if the purpose is to set limits for unwanted contamination. Using chronic feeding toxicity studies is problematic for estimating the toxicity of a drug given over a short period of time, although germane to the assessment of a food contaminant.

Information Resource Use

Deriving good exposure information is much simpler for a drug or biologic than for many other agents. Drugs are usually given under strictly controlled regimes. In addition, the companies making these products are required to perform studies on humans, reducing the problems associated with animal-to-man extrapolation. However, drugs are given to sick people, and often to very limited numbers with limited representation of sensitive subpopulations. In addition, drug toxicity studies are almost always of short duration, and considerations of toxicity are limited to a few years of follow-up.

For drugs and biologics, therefore, simple evaluation of clinical testing protocols is needed to estimate exposure. Toxicity information is estimated from human studies, complemented by a comprehensive program of postmarket surveillance to supplement information on toxicity.

Animal and short-term toxicity information is used as a guideline to help define the limits of the human exposures.

For devices, in addition to the necessity to consider the consequences of not using the device, there are special considerations of engineering aspects. Thus, the Devices Center utilizes information from materials science and physics to estimate the probability of failure. Much of this is proprietary data derived from studies performed by the companies attempting to sell the device.

The major focus of the assessment of risk associated with animal drugs concerns the residues of drugs in animal products and the risk to humans. Conceptually, they are treated similar to unwanted contaminants in food, thus the information needs are similar to those for the risks associated with food.

In considering the risks associated with foods, it is useful to appreciate that most of the FDA effort is traditionally concentrated on the handling and contaminants of foods. The natural constituents of food are considered safe by definition. This assumption is maintained despite the evidence of comparative epidemiology that approximately 35% of all preventable cancer in the United States is a result of natural food constituents (Doll and Peto 1981), and more recent evidence that calorie intake is the most significant factor in the modulation of induced and chronic toxicity, as well as spontaneous disease (Turturro and Hart 1991).

Example

To illustrate the information required for a risk assessment, consider one performed for a cosmetic color used mostly in lipstick (Hart et al. 1986). Risk assessment has two major components: exposure and toxicity. For cosmetic skin exposure, there are a number of factors to consider: for example, applica-

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tion, penetration, and both local skin effects and systemic effects. The keys to skin exposure to cosmetics are behavior and concentration. To evaluate the exposure to a compound in lipstick, such questions as how and how often it is applied and when it is used need to be answered. In evaluating these factors, we found little if any information on how many times lipstick is reapplied, its ingestion, or its absorption through the lips. The concentrations of the substances in the dyes used in the lipsticks were dependent on the particular lipstick being considered.

For toxicity, there was information on pure color, but very little on the complex formulations used in real life. This was ironic since the goal of risk assessment is to determine the risk of toxic agents under practical conditions of use and exposure. The information available was almost never on practical combinations of colors, or practical conditions of exposure.

When Is There Enough Data?

One important question in using information resources is the question of when there is enough data to make a decision. In trying to determine when there is enough data, it is important to understand that risk assessment is often not four steps in a hierarchical process but actually a compilation of information. One puts all that is known into a box and tries to organize the information. That's why there will never be enough data for a risk assessor; the more data there is available, the more data is used. An attempt is made to identify data gaps: glaring problems in making the extrapolations necessary to come to a conclusion.

An irony is that closing data gaps does not always result in a perceived increase in certainty. In the past, one was not necessarily aware of the many tacit assumptions about important factors used in risk assessment due to a lack of data and understanding. Often, questions related to pharmacokinetic and susceptibility differences in species and individuals, or problems in the response of a cell to an agent, were not even considered. Now as we are developing more information about the effect of an agent at the cell membrane, we become more and more aware of our lack of understanding. For example, there was an assumption that if a compound was carcinogenic in a rodent bioassay, it was carcinogenic in people. This assumption is now changing.

What should be understood is that any current problem with certainty is actually a problem in perception of uncertainty. In the past, risk assessors did not appreciate how uncertain they actually were. As we come to grips with the quantitation of risk and incorporate current information, we will be able to achieve a much more accurate representation of risk.

Conclusions

Information on exposure to compounds, with the exception of drugs and biological agents, is hard and expensive to attain; however, it is critical to efforts of understanding toxicity under practical conditions of use and exposure. Information allowing valid estimation of variability of

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"contaminants" is often missing, and, while extremely valuable, is expensive to obtain. Toxicity information in animals is often available for pure compounds, but people are almost never exposed to pure compounds and the effects of combinations of agents are relatively unknown.

It can be seen that there are obvious needs for comprehensive databases in a number of areas to assist risk assessment, especially in quantitating human exposure. Efforts to improve these relevant information sources will be very useful in improving accuracy and increasing the ability to conduct risk assessments.

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Risk Assessment Activities at NIOSH: Information Resources and Needs

Leslie T. Stayner, Theodore Meinhardt, Bryan Hardin,
National Institute for Occupational Safety and Health

Under the Occupational Safety and Health, and Mine Safety and Health Acts, the National Institute for Occupational Safety and Health (NIOSH) is charged with development of recommended occupational safety and health standards, and with conducting research to support the development of these standards. Thus, NIOSH has been actively involved in the analysis of risk associated with occupational exposures, and in the development of research information that is critical for the risk assessment process. NIOSH research programs and other information resources relevant to the risk assessment process are described in this paper. Future needs for information resources are also discussed.

Under both the Occupational Safety and Health Act (Public Law 91-596) and the Mine Safety and Health Act (Public Law 95-164), the National Institute for Occupational Safety and Health (NIOSH) is charged with developing recommended occupational safety and health standards, and conducting research to support development of those recommended standards. NIOSH regards risk assessment as a critical element in its decision logic for making recommendations for standards when suitable data is available. Although NIOSH has only limited regulatory authority (pertaining to the testing and certification of respirators and coal mine dust samplers), the Institute's research, recommendations and risk analysis have had a substantial impact on the regulatory actions of a number of agencies such as the Occupational Safety and Health Administration (OSHA), the Mine Safety and Health Administration (MSHA), and the Environmental Protection Agency.

Occupational safety and health hazards are evaluated on a case-by-case basis. To develop a recommended standard, NIOSH performs a comprehensive assessment of all relevant research information and, when possible, a quantitative risk assessment. The Institute's recommendations with the accompanying detailed analysis are published as Criteria Documents and Current Intelligence Bulletins. Less detailed analyses, focused on specific injury or disease occurrences, may be published as Alerts or in other publications. These publications are formally transmitted to OSHA and MSHA in accordance with requirements of the Occupational Safety and Health Act and the Mine Safety and Health Act.

NIOSH regards risk assessment as a critical element in its decision logic for making recommendations for standards.

The Institute's recommendations are published as Criteria Documents and Current Intelligence Bulletins.

The purpose of the Occupational Safety and Health Act is ". . . to assure so far as possible every working man and woman in the Nation safe and healthful working conditions. . ." (Section 2(b)). The Act further charges NIOSH, acting for the Secretary of Health and Human Services,

to "... describe exposure levels that are safe for various periods of employment, including but not limited to the exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience." (Section 20(a)(3)). Similar language is contained in the Mine Safety and Health Act. NIOSH regards these statements as legislatively mandated policy that guides its assessment of risk.

Much of the data generated by NIOSH research activities is relevant for risk assessment purposes. Generally these research efforts address one of the components of the risk assessment process: hazard identification, exposure assessment, dose-response assessment, or risk characterization.

NIOSH consists of three offices and seven divisions. The Division of Surveillance, Hazard Evaluations, and Field Studies (DSHEFS), the Division of Respiratory Disease Studies (DRDS), and the Division of Safety Research (DSR) are responsible for major surveillance and epidemiologic efforts to identify work-related safety and health problems and the associated risk factors. The Division of Biomedical and Behavioral Sciences (DBBS) participates in these investigations by assisting with biological monitoring and by developing and applying improved techniques for characterizing other biological (neurobehavioral, immunological, psychological) indicators of exposure or effect. DBBS also conducts worksite investigations when physical agents, psychological stress, or ergonomic problems are the primary concern.

DSR conducts worksite investigations of selected traumatic occupational fatalities, including those resulting from exposures to toxic substances in confined spaces such as tanks and manholes. This investigative activity is known as the Fatal Accident Circumstance and Epidemiology (FACE) project. In addition to being a hazard identification activity, FACE enables the study of factors that may contribute to worker risk, and the development and communication of risk management options for controlling those factors. Information on risk and risk management is communicated to safety and health professionals, and other managers of workplace risk.

DSHEFS has primary responsibility, with the collaboration of DRDS, DSR, DBBS, and the Division of Physical Sciences and Engineering (DPSE), for a research and service program that provides a health hazard evaluation (HHE) in any workplace when requested by any employer, employee representative, or group of 3 or more employees. In an HHE, a team of NIOSH scientists investigates suspected safety or health hazards in the workplace. Upon completion of the investigation, both the employer and the employees are provided with a written report in which any hazards identified are discussed and remedial actions are recommended. If violations of OSHA standards are revealed by the HHE, the written report is also provided to the OSHA Regional Office, often resulting in a follow-up inspection by OSHA. DSHEFS also

These research efforts address one of the components of the risk assessment process: hazard identification, exposure assessment, dose-response assessment, or risk characterization.

DSR conducts worksite investigations of selected traumatic occupational fatalities, including those resulting from exposures to toxic substances in confined spaces such as tanks and manholes.

has primary responsibility for the conduct of industry-wide studies which are in-depth epidemiologic studies of the association between occupational exposures and disease. These studies generally attempt to relate exposure information with health outcomes, and are thus an invaluable source of dose-response information in addition to providing information for hazard identification.

DBBS and DRDS also conduct laboratory research programs that contribute to hazard identification and develop exposure-response data from in vitro and in vivo research in mammalian or non-mammalian systems. These programs also investigate underlying mechanisms of disease and injury causation. Human responses in limited, controlled laboratory studies are also undertaken, for example, to evaluate the adequacy of current exposure limits for chemicals or margins of safety in controlling for pre-clinical signs of potential problems.

DPSE conducts substantial laboratory and field research relating to sampling and analytical techniques and engineering control technology. These activities contribute primarily to risk management by improving existing and developing new options for exposure measurement and control. Other information ultimately contributing to risk management is developed by research programs in DSR on personal protective equipment, including respirators, protective clothing, gloves, and safety devices.

DSHEFS, DRDS, and DSR are involved in several surveillance activities that are aimed at the detection and monitoring of disease and injury trends, as well as the efficaciousness of regulatory activities to control these hazards.

The Division of Training and Manpower Development (DTMD) is primarily involved in activities related to the training of professionals in occupational health and safety through courses that it offers and through the Educational Resource Centers (ERC) program. However, DTMD has recently developed a research effort to evaluate the effectiveness of training programs as a prevention strategy.

The Division of Standards Development and Technology Transfer (DSDTT) is responsible for producing the Institute policy recommendations and regulatory responses. In fulfilling these tasks, DSDTT serves as the bridge connecting the Institute and its research divisions with the regulatory agencies and the public. DSDTT is responsible for integrating all of these internal sources of information and expertise with external sources to develop comprehensive analyses of risk as the basis for policy recommendations. When suitable data are available, the DSDTT risk assessment unit performs a quantitative risk assessment. This may be a part of the comprehensive analysis of a Criteria Document, or may be developed in response to OSHA or MSHA proposed rulemaking.

These analyses and recommendations are set forth in NIOSH policy documents, usually in the format of a Criteria Document or a Current Intelligence Bulletin. DSDTT is currently involved in conducting assessments of the lung cancer risks associated with

DSHEFS has primary responsibility for the conduct of industry-wide studies which are in-depth epidemiologic studies of the association between occupational exposures and disease.

Several surveillance activities are aimed at the detection and monitoring of disease and injury trends.

exposure to diesel exhaust in mines, and to cadmium. DSDTT has also been involved in the development of physiologically-based and pharmacodynamic risk assessment models for cancer and noncancer outcomes through a collaborative agreement with researchers at the Massachusetts Institute of Technology (MIT).

NIOSH technical reports and journal publications produced from the research efforts previously described are an extremely useful source of information for risk assessment efforts and have been used extensively by NIOSH and other agencies for this purpose. These journal articles may be obtained by contacting the NIOSH research divisions involved, and the technical reports may be obtained by contacting the publications office (513-533-8287).

DSDTT maintains three major data bases: 1) RTECS is the world's largest registry of toxic chemicals covering over 100,000 chemicals; 2) NIOSHTIC is an on-line bibliographic system containing over 160,000 abstracts, emphasizing occupational, environmental, and historical literature; and 3) the Document Information Directory System (DIDS) is a directory of all NIOSH-generated publications and reports.

DSHEFS maintains the National Occupational Exposure Survey (NOES) data base and related files derived from a representative sampling of the characteristics of workplaces throughout the country. DSHEFS has also created an Occupational Mortality Surveillance Data Base (OMSD) which contains occupational and cause of death information coded from death certificates from 23 states between 1979-1987. The OMSD may be a useful source of information for hazard identification, although more refined epidemiologic studies will generally be needed to confirm the hypotheses generated from this data base. DSR maintains the National Traumatic Occupational Fatality (NTOF) data base and FACE data bases. The NTOF data base is a national census of occupational fatalities developed using death certificate information obtained from the entire United States population. NTOF data are currently available for the years 1980-1986. The FACE data base is a compilation of data from over 300 worksite investigations of selected occupational fatalities. DRDS maintains two data bases that consist of the National Occupational Exposure Survey in Mines (NOESM), which is the equivalent of NOES for mining environments, and the X-ray Surveillance Program data base, which is a collection of X-ray and occupational data on underground coal miners.

Clearly, epidemiologic information provides the best basis for estimating the risks for health effects among human populations exposed to hazardous conditions at work and elsewhere. Unfortunately, suitable information from human studies is often unavailable and risk assessors must rely on animal bioassay information to estimate human risks. Better exposure information for estimating dose-response relationships in epidemiologic studies and for estimating the extent of exposure among working populations is also sorely needed. NIOSH is actively involved in the development of

DSDTT serves as the bridge connecting the Institute and its research divisions with the regulatory agencies and the public.

DSDTT maintains three major data bases.

biologic markers which should provide a better understanding of the relationship between delivered dose (exposure) and the dose at the target organ (biologic dose). Finally, the development of pharmacodynamic and physiologically-based models offer great potential for improving interspecies extrapolations. However, there is clearly a great need for additional information on the basic kinetic and physiological data that are used in these models, particularly for humans.

Summary

NIOSH views quantitative risk assessment as an important element in the development of recommendations for occupational health standards. The Institute is involved in a wide range of research activities that provide information relevant to all of the components of the risk assessment process.

Through these research efforts NIOSH has developed an extensive data base, which of course is available to other agencies and the public. Future risk assessment activities at NIOSH will be focused on developing better methods for risk characterization through improvements of exposure characterization in epidemiologic studies, and through the incorporation of biologic markers, and physiologic and pharmacodynamic information in the risk assessment process.

Suitable information from human studies is often unavailable and risk assessors must rely on animal bioassay information to estimate human risks.

National Toxicology Program Chemical Nomination and Selection Process

James K. Selkirk, National Institute of Environmental Health Sciences

The National Toxicology Program (NTP) was organized to support national public health programs by initiating research designed to understand the physiological, metabolic, and genetic basis for chemical toxicity. The primary mandated responsibilities of NTP were in vivo and in vitro toxicity testing of potentially hazardous chemicals; broadening the spectrum of toxicological information on known hazardous chemicals; validating current toxicological assay systems as well as developing new and innovative toxicity testing technology; and rapidly communicating test results to government agencies with regulatory responsibilities and to the medical and scientific communities.

During the 1970s, several federal government agencies independently engaged in toxicity testing. It became clear that a unified program was necessary to avoid duplication and to respond to (1) the need for standardized toxicology testing methods and (2) the broadening range of diagnostic assays used in the evaluation of chemicals suspected of being hazardous to humans. In 1978 the Secretary of the Department of Health, Education, and Welfare (HEW) responded to this need by forming the NTP which is composed of specially designated sections of several federal agencies. Members included the National Institute of Environmental Health Sciences (NIEHS), the Center for Disease Control's National Institute for Occupational Safety and Health, and the Food and Drug Administration's National Center for Toxicological Research. The NTP was organized to support national public health programs by initiating research designed to understand the physiological, metabolic, and genetic basis for chemical toxicity.

The primary mandated responsibilities of NTP were in vivo and in vitro toxicity testing of potentially hazardous chemicals; broadening the spectrum of toxicological information on known hazardous chemicals; validating current toxicological assay systems as well as developing new and innovative toxicity testing technology; and rapidly communicating test results to government agencies with regulatory responsibilities and to the medical and scientific communities. These important duties are still the driving principles of NTP.

A unified program was necessary to avoid duplication.

In 1981, Dr. David Rall, director of the NIEHS became the director of NTP, and management of the program moved from the National Cancer Institute in Bethesda, Maryland, to Research Triangle Park, North Carolina. Although studies in the early years of the program were primarily designed as straightforward tumor bioassays, the last decade has seen the NTP program grow in range, scope, and sophistication, along with advances in basic toxicologic knowledge. In addition, NIEHS scientists are readily available to

The last decade has seen the NTP program grow in range, scope, and sophistication, along with advances in basic toxicologic knowledge.

assist regulatory agencies by maintaining direct communication with regulatory agency staff for consultation. NTP scientists routinely confer on study designs that will aid in risk assessment and in decision making toward the development of federal regulations for controlling chemical exposures in the workplace and the general environment. Because NTP is a consortium of several federal agencies, the administrative infrastructure is designed to interact with, as well as seek advice from all federal agencies that are actively engaged in or require knowledge of chemical toxicity. Figure 1 outlines the way in which NTP management is coordinated through several interagency committees. The two NTP governing bodies are the Executive Committee, whose members are the senior administrators of major federal government public health agencies, and a Board of Scientific Counselors (BSC), which is composed of nongovernment experts in various fields of toxicology. These two committees meet several times a year to hear progress reports of research programs of the various components of NTP and to discuss individual agency needs. The Steering Committee is composed of senior staff members of NTP agencies and meets regularly to review ongoing toxicology studies at the various NTP research facilities.

In addition, special committees function to support various aspects of the NTP program. The Chemical Evaluation Committee (CEC) receives and reviews nominations of chemicals for testing and makes recommendations to the NTP Executive Committee.

The Annual Reports on Carcinogens working group is mandated by Public Law 95-622 to publish a list of substances (1) that may be reasonably anticipated to be carcinogens, (2) to which a significant number of persons residing in the United States are exposed, and (3) for which no exposure standard is established. The subcommittee on Data Audits is composed of NTP member agency staff and has a more ad hoc function since it meets only by special request. Reproductive studies are reviewed by a special subcommittee of experts that report directly to the BSC.

The final product of NTP toxicity studies is a comprehensive summary of all toxicological assays performed on a given

NTP, a consortium of several federal agencies, is designed to interact with, as well as seek advice from all federal agencies that are actively engaged in or require knowledge of chemical toxicity.

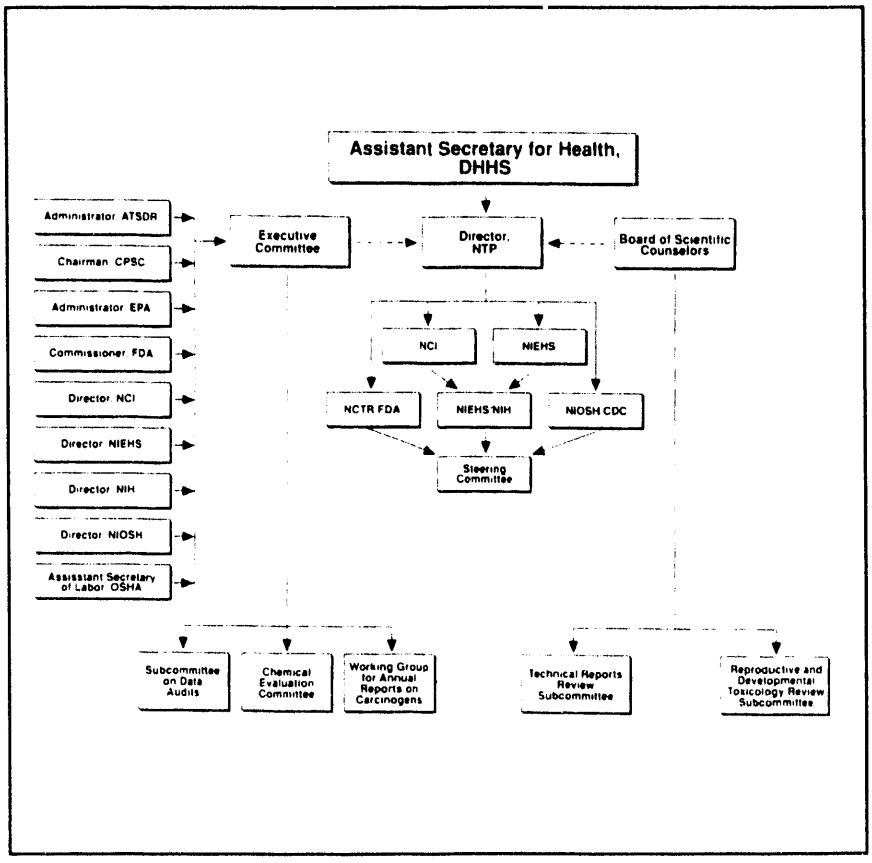

Fig. 1. Organizational management of the National Toxicology Program.

chemical. The Technical Reports Sub-Committee consists of members of the BSC as well as nongovernment experts in various toxicology disciplines. The technical report meetings are announced in the *Federal Register* and are held in open public session. Comments are invited from all interested parties. The technical report then becomes a permanent record and is available through the National Technical Information Service.

Figure 2 summarizes the NTP chemical nomination and selection process. Although the major source of nominations historically has been government agencies, chemicals can be recommended for testing by any individual who suspects that a chemical may be a health hazard. The NTP Chemical Selection Coordinator receives nominations and is responsible for preparing an information package (Executive Summary) on the nominated chemical for review by CEC. If the committee decides that current information is insufficient to determine the degree of potential hazard to humans and accepts the chemical for testing, a *Federal Register* notice is published, and any individual (or organization) who may have information not available in the open literature is invited to submit it for NTP consideration. Alternatively, CEC may decide the available toxicologic information is suggestive of a hazard but insufficient to draw a conclusion. It may recommend some preliminary testing such as in vitro genetic toxicology to help in the preliminary hazard assessment. Once completed, the results cycle back to the recommending agency for review and a committee decision is made whether to continue toward full toxicological analysis of the chemical. The amended Executive Summary, along with the rationale for deciding to undergo more extensive testing of the chemical, is reviewed by both the Executive Committee and the BSC. If all agree to proceed to the testing phase, the Steering Committee decides which NTP agency will be responsible for developing the test protocol. The final test protocol is subject to review by the Toxicology Design Review Committee, which is composed of NTP staff scientists, for confirmation that the planned assays meet all the needs of the NTP member agencies. Once the protocol is approved, the chemical enters the in-depth evaluation phase.

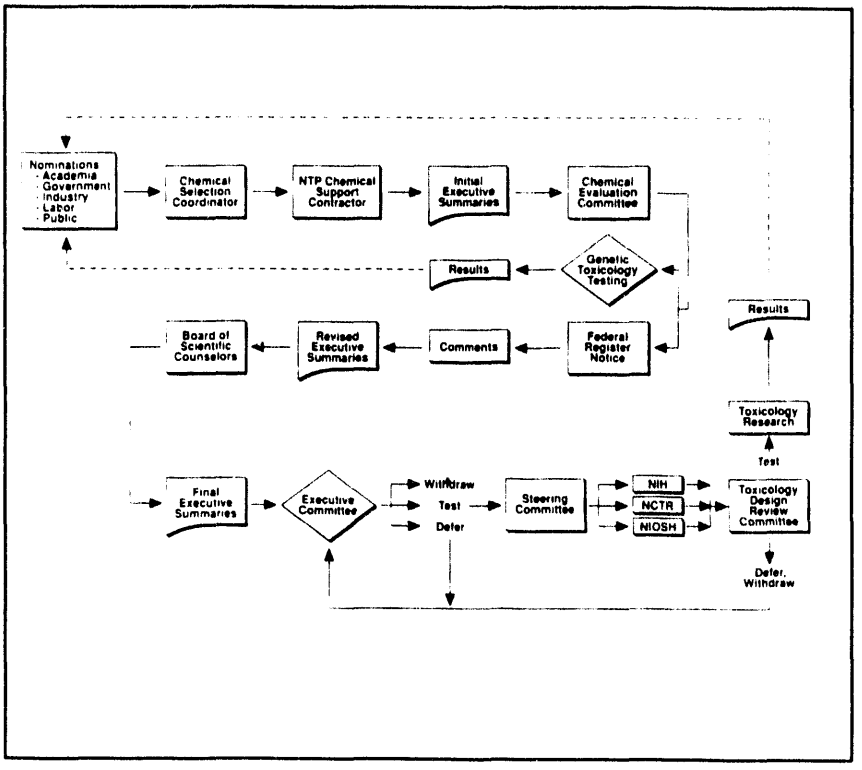

Fig. 2. Pathway for nomination and selection of chemicals for testing in the National Toxicology Program.

If the committee decides that current information is insufficient to determine the degree of potential hazard to humans and accepts the chemical for testing, a Federal Register notice is published, and any individual (or organization) who may have information not available in the open literature is invited to submit it for NTP consideration.

In most cases, short-term in vivo tests are performed first to determine the metabolism and disposition of the chemical, locate target organs, and develop a suitable dosing regime to complete a chronic 2-year bioassay. Usually, 2 weeks or 90 day, short-term assays are conducted, the latter being followed up with extensive tissue and organ histopathology to localize damaging chemical effects. This 90-day tissue analysis sets the stage for the chronic study because it usually yields clues about where the chemical will probably exhibit its toxicity. Clinical chemistries are also performed at key times during the short-term assays to assess the metabolic effect of the chemical on the animals' intermediary metabolism, kidney, and liver function. The chronic study lasts 104 weeks and is followed by an extensive review of all the data and a determination of carcinogenicity of the chemical. The conclusions are peer reviewed by a panel of outside experts in public session, and a final Technical Report is published and made available through the Government Printing Office.

Ninety-day tissue analysis sets the stage for the chronic study because it usually yields clues about where the chemical will probably exhibit its toxicity.

Assessing Human Health Risk in the USDA Forest Service

Dennis R. Hamel, U.S. Department of Agriculture—Forest Service

This paper identifies the kinds of risk assessments being done by or for the U.S. Department of Agriculture (USDA) Forest Service. Summaries of data sources currently in use and the pesticide risk assessments completed by the agency or its contractors are discussed. An overview is provided of the agency's standard operating procedures for the conduct of toxicological, ecological, environmental fate, and human health risk assessments.

Since the beginning of mankind, men and women have struggled to feed, clothe, and house themselves. The first tools used were manual; however, through time, alternatives including the use of chemicals, began to emerge. In agriculture and forestry, a new era ensued, and as the use of chemicals increased, so did questions about their effects on human health and the environment. In time, a process of risk assessment was developed to deal with these questions.

Risk assessment takes many forms. Practitioners use varying definitions to describe the components of risk assessment. In the USDA Forest Service, we sometimes use the terms risk analysis and risk assessment interchangeably, but for the most part, we use risk analysis to describe the process and risk assessment to describe the documentation.

Most USDA Forest Service risk assessment documents have been prepared in compliance with the National Environmental Policy Act (NEPA). They relate to the use of pesticides in forestry. This use is minor, accounting for less than 1% of all the pesticide use in the United States. All pesticide use must comply with the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, which is administered by the U.S. Environmental Protection Agency (EPA).

The USDA Forest Service pesticide policy is covered in Forest Service Manual (FSM) 2150, Pesticide Use, Management, and Coordination. In addition to this policy document, the agency has compiled companion guidelines in a handbook that has the same title. The contents of the chapter on risk analysis procedures includes components of risk analysis, hazard analysis, exposure analysis, and risk characterization. That of Hazard Analysis includes Hazard Analysis, Sources of Toxicity Information, Types of Human Toxicity Studies, and Types of Other Organism Toxicity Studies. The sections under Exposure Analysis include Exposure Analysis, Factors Affecting Human and Environmental Exposure, Potential Routes of Exposure, Exposure to Workers, Exposure to the Public, and Exposure Scenarios.

Most USDA Forest Service risk assessment documents relate to the use of pesticides in forestry.

The USDA Forest Service pesticide policy is covered in FSM 2150, Pesticide Use, Management, and Coordination.

In addition, the former Council on Environmental Quality (CEQ) regulations required that if information was incomplete or unavailable, federal agencies must do a worst-case analysis. This is no longer a requirement of CEQ, but the Forest Service continues to do them under the proposed name of catastrophic event scenarios. Their purpose is to:

- determine if information is missing and if it is relevant to making a reasoned choice among alternatives,
- identify the cost of obtaining the missing information,
- determine if alternative scenarios are generally acknowledged as scientifically reasonable,
- evaluate the state of the art to collect the missing data, and
- indicate the probability of occurrence.

Finally, we conduct risk characterization that includes dose estimation, evaluation, and documentation.

You may be asking, "where does the Forest Service obtain information to assess health risks?" The answer is that, primarily, we obtain information from the EPA using their reregistration standards, science chapters, *Tox One Liners*, fact sheets, etc. The Forest Service reformats this information to fit forestry-use situations and documents it in risk assessments.

If information is incomplete or unavailable, the forest service does a worst-case analysis.

The agency also contracts with independent sources who use databases such as MEDLINE, EMBASE (Excerpta Medica), TOXLINE, the Hazardous Substances Data Bank, the Registry of Toxic Effects of Chemical Substances, the International Pharmaceutical Abstract Database, and the Chemical Carcinogenesis Research and Information System to collect, collate, and interpret data for assessing human health risk.

In summary, Gifford Pinchot, first Chief of the Forest Service said, "Conservation is the foresighted utilization, preservation, and/or renewal of forest, waters, lands, and minerals for the greatest good of the greatest number for the longest time." To accomplish this mission, the Forest Service has determined that chemicals, including pesticides, play a minor but important role and that we have a responsibility to use all available data to assess the potential impacts of their use on human health.

Primarily, we obtain information from the EPA using their reregistration standards, science chapters, Tox One Liners, fact sheets, etc.

Access and Use of Information Resources in Assessing Health Risks from Chemicals in Food

Wesley A. Johnson, U.S. Department of Agriculture

The Food Safety and Inspection Service (FSIS) is responsible for the wholesomeness, safety, and adulteration-free status of meat and poultry. The agency developed the National Residue Program (NRP) to monitor these products for residue of drugs, pesticides, and environmental contaminants. Today, few chemical residues are detected in meat and poultry because of the success of the NRP.

The National Residue Program (NRP) Plan is developed yearly to monitor for chemical residues in both domestically produced and imported meat and poultry. The randomly selected samples are analyzed at one of the FSIS or contract chemistry laboratories. The laboratory testing results along with other information are used by FSIS for exposure assessment to characterize and manage the risks of adverse effects to human health from consumption of meat or poultry.

FSIS uses all available information resources for its risk assessment and risk management decisions at points such as the following:

1. Compound identification,
2. Compound Evaluation System (CES) rank,
3. Compounds included in the NRP, and
4. Detection method development recommendations.

Each chemical has a time line or history of use and regulatory activity. (See Fig. 1.) A compound's time line depicts the sequence of decisions (in boxes) that require FSIS (above line) to use information resources to make assessments for residue occurrence in meat and poultry. Each of the steps in the sequence will be discussed as to how information resources are used. Regulatory activity by other agencies (below line), such as tolerance setting and banning, are indicated on the time line.

Databases, journal articles, general reference materials, and reports are used by FSIS to identify compounds that are of concern. Compound tolerance-setting reports from the U.S. Environmental Protection

Laboratory testing results are used by FSIS for exposure assessment to characterize and manage the risks of adverse effects to human health from consumption of meat or poultry.

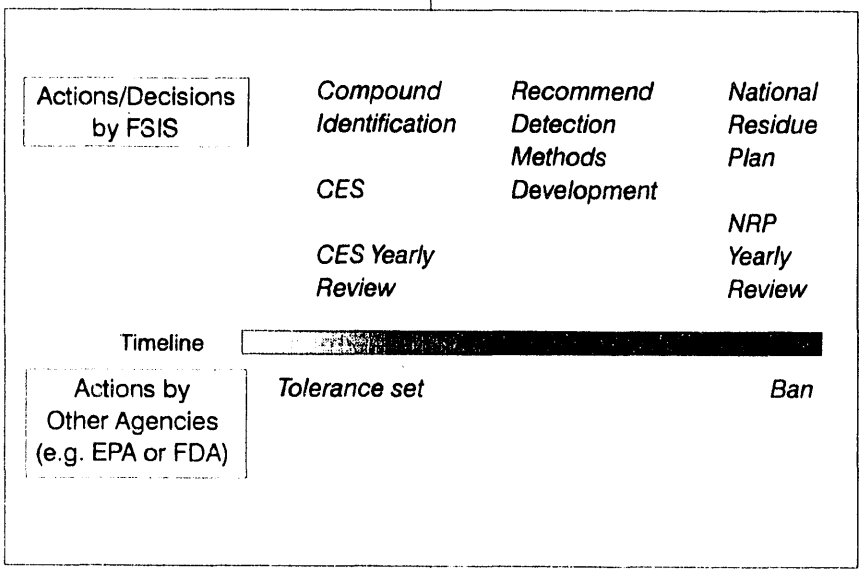

Fig. 1. Compound history time line.

Agency (EPA) and the Food and Drug Administration (FDA) are the primary sources of information for identification of compounds of concern. The setting of a tolerance for a compound in animal tissues occurs after considerable evaluation activity by EPA or FDA and triggers FSIS actions. A compound that produces a residue in meat or poultry and has adverse effects on human health is a compound of concern for further evaluation.

Minimum health safety regulations were required for the use of many drugs and pesticides in the past. Some compounds are no longer used but persist in the environment, while others are still in use. FSIS is actively investigating both of these classes of compounds. Dibutyltin dilaurate is an example of a compound that has been in use but has had little regulatory activity. During the past 3 years, FSIS evaluated and developed chemical detection methods and successfully controlled residues from this drug. This is an exciting example of excellent work done by FSIS. There are also examples of compounds that produce residues and have been banned because of their risk characterization.

FSIS, along with producers, the Extension Service, and other federal agencies, has been instrumental in lowering the residue violation rate by a factor of ten over the past 20 years. Consequently, FSIS is changing its strategy to identify and sample remaining populations of animals with significant concentrations of chemical residue. FSIS is identifying variables that are common to populations of animals with drug or pesticide residues. Once the variables are identified, the animal populations associated with these variables will be targeted for appropriate residue surveillance.

FSIS is changing its strategy to identify and sample remaining populations of animals with significant concentrations of chemical residue.

Compound Evaluation System Rank

FSIS uses the CES as its risk assessment procedure. Information about the first two steps in this risk assessment, hazard identification and dose response assessment, is available from FDA and EPA if a tolerance for the compound in meat and poultry has been set. FSIS is able to identify drugs and pesticides that are of concern by using the results of these two steps. FSIS divides exposure assessment into two parts. First, the approved uses of drugs and pesticides of concern are evaluated for potential animal exposure. Positive animal exposure assessment dictates the use of pharmacokinetics to predict whether the compound produces a residue in meat or poultry. A compound with positive animal exposure that also produces a residue in meat and poultry is evaluated for potential exposure to humans. These data are used to characterize the risk of an adverse effect to human health from consumption of meat or poultry In addition, the yearly results from the NRP sampling and testing are used to update the exposure assessment and risk characterization for each animal slaughter class-compound pair.

The CES rank of compounds is based on the severity of human effects and the frequency at which humans may be exposed.

The CES rank of compounds is based on the severity of human effects and the frequency at which humans may be exposed. A two-tiered hierarchical system is used. Roughly, hazard is ranked as follows: A = high

human health hazard, B = medium human health hazard, C = low human hazard, D = negligible effect, and Z = unknown. The rank for frequency of exposure to these compounds in meat or poultry is based on the likelihood of a person consuming a toxic dose in meat or poultry. These ranks are: 1 = high probability, 2 = medium probability, 3 = low probability, 4 = negligible probability, and Z = unknown.

The following is a quote from the Compound Evaluation System.

"There are more than 300 pesticides approved for use in the United States, with varying potential for their occurrence as residues in meat and poultry. There are many others that may also occur as a result of environmental contamination or in imported foods from significant use in other countries. The number of potential residues from animal drugs and biologics is equally impressive, again with the foreign use of compounds adding to the total number of residues that may occur in meat and poultry. The potent biological activity of many of these compounds raises concern regarding the potential hazard to human health associated with the ingestion of meat and poultry containing residues from pesticides, drugs, or other chemicals.

"Clearly, it is neither feasible nor necessary to monitor for residues of all chemicals that could contaminate meat and poultry. However, in deciding which available resources and monitoring efforts should be assigned, it is imperative that FSIS can assess relative concerns for those residues most likely to have the greatest impact on public health. To assist the agency in the effective management of its resources and residue program activities, a compound evaluation system was developed."

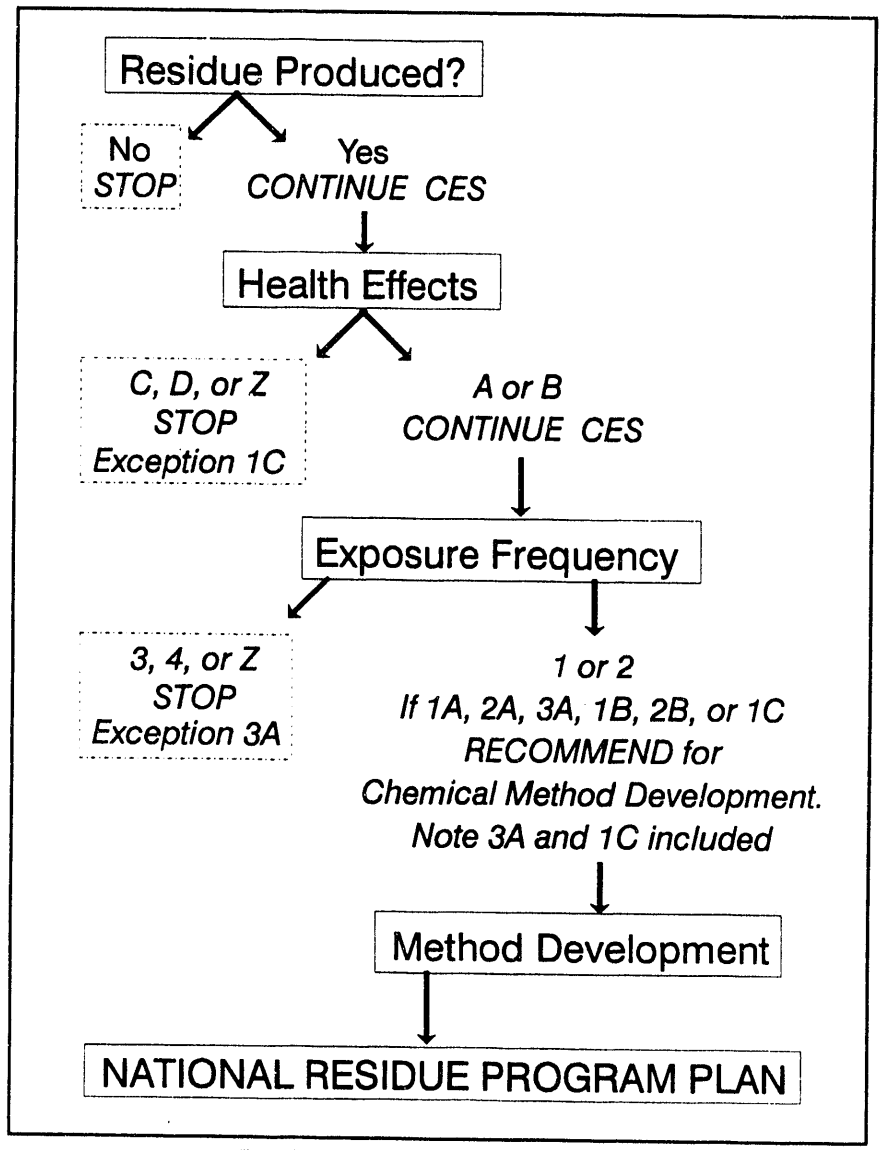

Fig. 2. The CES risk assessment process.

The following are some of the databases searched for completion of a risk assessment under CES.

Agricola 79 +
Agris
Agrochem Handbook
Biosis 1969 +

CAB Abstracts
Cancerlit
CA Search
Chem Industry Notes
Chemical Exposure
Chemname
Compendex Plus
Conf Papers Index
CRIS/USDA
Embase
Enviroline
Enviro Perio Bib
Federal Research In Progress
Food adlibra
Food Sci & Tech Abstracts
GPO Monthly Cat
HSDB
IRIS
Kirk Othmer Online
Life Sciences Coll
Medline
NTIS
NTP Chemtrack
Pollution Abs
Toxline
TSCA Inventory

Compounds Included in the National Residue Program Plan

The NRP is designed to randomly sample the national herd and test for residues by animal slaughter class and compound pair. The national herd is divided into 19 animal slaughter classes for residue testing. Compounds are added to the NRP based on the following:

1. the compound must produce a residue in meat or poultry;
2. the compound must be ranked according to the CES as A1, A2, A3, B1, B2, or C1; and
3. a regulatory method for detection must be in the FSIS laboratory.

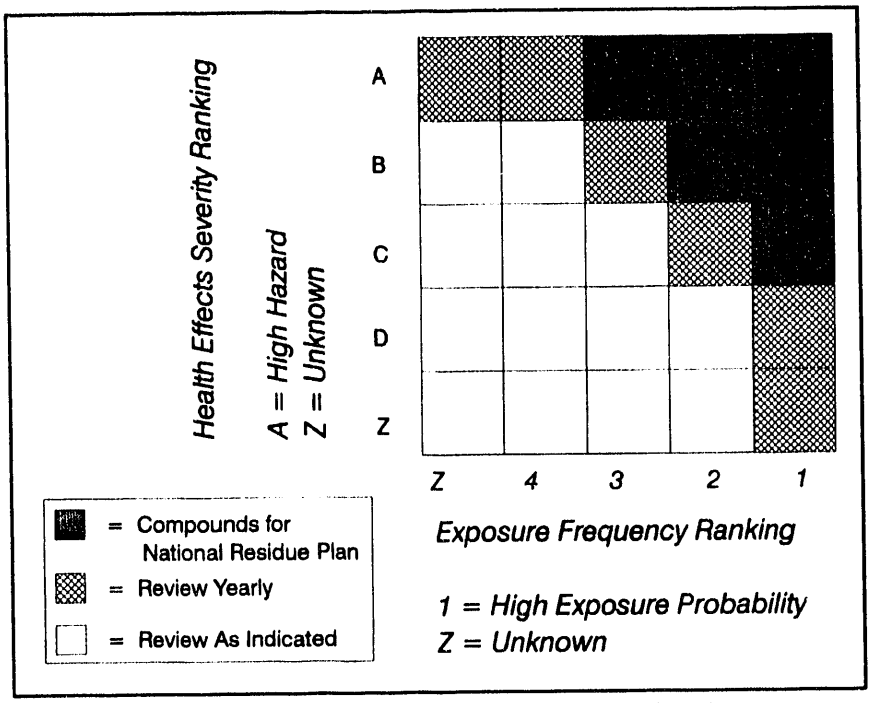

Fig. 3. Compound criteria for national residue plan.

The residue testing of the 19 slaughter classes is divided into the following:

1. Monitoring phase - The monitoring phase is designed to randomly sample and test for the presence of concentrations above tolerance for compounds of concern in the national herd on a yearly basis.
2. Surveillance phase - In this phase biased sampling is used to investigate and control the movement of potentially adulterated product.
3. Exploratory phase - Regulatory actions are not used in this phase. Information gathering is one reason for including an animal class-compound pair under this phase. The recommendations for development of detection methods for dibutyltin dilaurate were made based on information from this phase.

The National Residue Program Plan is designed to randomly sample the national herd and test for residues by animal slaughter class and compound pair.

Detection Method Development Recommendations

The Residue Evaluation and Planning Division recommends methods development for compounds satisfying the NRP requirements. This activity continues throughout the year. FSIS uses practical analytical methods for detecting chemical residues in concentrations greater than tolerance in meat and poultry. Multiple sources of information are required to satisfy the criteria used as guidelines for methods suitable for regulatory use.

Summary

The Food Safety and Inspection Service randomly samples the national herd for the presence of drug, pesticide, and environmental contaminant residues. The animal slaughter class-compound pair samples are selected because of an assessed risk of adverse human health effect from consumption of this slaughter class with residues of the compound. The analytical results from these samples represent a considerable amount of data for exposure assessment; these results and other new information update the risk characterizations of compounds in the FSIS risk assessment process.

The animal slaughter class- compound pair samples are selected because of an assessed risk of adverse human health effect from consumption of this slaughter class with residues of the compound.

How Information Resources are Used by Federal Agencies in Risk Assessment Application: Rapporteur Summary

Penelope Fenner-Crisp, U.S. Environmental Protection Agency

The application of information available for risk assessment from the federal perspective is described. Different federal agencies conduct varying degrees of hazard evaluation, and some also generate empirical data. The role of the Agency for Toxic Substances and Disease Registry in hazard assessments of potential public health impacts of Superfund sites includes identification of the 275 most significant substances. ATSDR is responsible for preparing toxicological profiles. ATSDR also identifies data gaps and needs critical to adequately assessing human health impacts.

There are those who for some time have been predicting the demise of the concept of risk assessment as we know and define it today. They cite as evidence the trend toward development of legislation that dictates the use of technology-based rather than risk-based regulatory solutions and/or proscriptive elements to risk assessment methodology. We have examples of this on both the federal and state levels. On the state level, an example is California's Proposition 65 and Big Green, the Environmental Protection Act of 1990. On the federal level, aspects of this occur in the Clean Air Act and in ongoing discussions about food safety legislation that would impact both EPA and the Food and Drug Administration. If this prediction is on target, participants in this conference are either ignorant of the forecast, are choosing to ignore it, or know something is false about the assertion. Several representatives from federal and state agencies earlier described how they use information on hazard, exposure, and risk in their own work. The presenters' intention apparently is to continue using this kind of information because they have practical applications for it. The presenters said that the roles of the federal agencies in the risk assessment process varied. Jim Selkirk at the National Toxicology Program (NTP), Leslie Stayner at the National Institute for Occupational Safety & Health (NIOSH), and Angelo Turturro representing the National Center for Toxicological Research (NCTR), all are from agencies that generate empirical data primarily for other organizations to use. Other agencies have active risk assessment roles although perhaps not in the regulatory sense. An example of this is the way the U.S. Forest Service, as described by Dennis Hamel, uses information on pesticides when choosing them for application in the field.

Some predict the demise of the concept of risk assessment as we know it.

Other agencies have active risk assessment roles although perhaps not in the regulatory sense.

As previously mentioned, NIOSH generates empirical data and does some risk assessments. Also, over the years it has done hazard assessment in developing criteria documents and bulletins

for use by the Occupational Safety and Health Administration (OSHA), and other organizations with respect to the occupational setting. The Agency for Toxic Substances and Disease Registry (ATSDR) Toxicology Division's responsibilities include the gathering of hazard, dose response, exposure, and epidemiologic data for the development of toxicological profiles in support of EPA's Superfund Program. Some agencies' responsibilities include cleanup of hazardous waste sites. The Army and Department of Energy presentations noted that each has responsibilities for assessing and cleaning up hazardous waste sites on federal properties. Therefore, they too conduct their own risk assessments, making use of the various types of hazard assessment and risk assessment information available. In fact, Major Legg called the Army the "olive-drab EPA."

Additionally, some agencies have enforcement responsibilities. For instance, Dr. Turturro spoke of the centers within the FDA that are responsible for food, drugs, cosmetics, medical devices, biologics, etc., each center having its own set of regulatory responsibilities. The Food Safety and Inspection Service of the U.S. Dept. of Agriculture (USDA) is responsible for monitoring our meat, milk, and poultry for excess or unsanctioned residues of pesticides or drugs. Lastly, EPA has several environmental laws to enforce. Many EPA regulations were developed using the risk assessment process.

Each presenter stressed the need for good databases (good in the sense of having adequate and quality-assured data) containing as much data as possible, and having mechanisms by which these data may be accessed easily by potential users. With 50 states and a number of federal agencies generating these data and storing them in a variety of databases, it is easy to see why there may be no common basis for access. We in the federal government, and I assume those in state government too, are often castigated about redundancy: that we have multiple avenues for generating and storing essentially the same information is not a particularly efficient expenditure of monies. The processes that we have been talking about at this conference suggest that some of that redundancy can be excised and that we can be more efficient in the ways we gather and communicate information.

The need for good databases is stressed.

ATSDR provides public health assessments that address the health impacts of Superfund sites to EPA's Office of Emergency and Remedial Response.

As a part of this process, Title I, Section 110, of the Superfund Amendments of 1986 directs the ATSDR to develop programs in three areas: listing of hazardous substances, preparation of toxicological profiles, and identification of data gaps and the implementation of necessary research to fill priority data needs. The first of these areas is the listing of the 275 most "significant" substances occurring at Superfund sites based upon their frequency of occurrence, inherent toxicity, and potential for human exposure. ATSDR is responsible for preparing toxicological profiles, in which the information necessary to assess

ASTDR is responsible for preparing toxicological profiles in which the information necessary to assess the public health consequences of the listed chemicals is collected and summarized.

the public health consequences of the listed chemicals is collected and summarized.

ATSDR also identifies data gaps that should be filled for a thorough assessment of the human health impact of these chemicals. Secondary to this is identification of priority data needs that are critical to adequately assess human health impacts. To date 117 priority data needs have been identified for 38 chemical substances.

As anticipated, questions arose regarding the funding and scheduling of testing. A directive in the law addresses this situation, particularly with respect to testing requirements in negotiated testing agreements with affected industry or other funding sources. It also addresses the use of National Institute of Environmental Health Sciences (NIEHS), NTP, or other federal agencies to fill research needs that do not easily lend themselves to the use of testing authorities such as the Toxic Substances Control Act or the Federal Insecticide Fungicide and Rodenticide Act.

We have a lot of hazard-related data that is used for hazard identification and dose-response assessment. We haven't talked about it much here, but quite often when using the same hazard-related data, various agencies come to different conclusions. One would expect differences to occur with respect to the exposure data because we usually are focusing on a particular exposure scenario for which we are developing a risk assessment. However, one can ask whether the hazard assessment should be different. Efforts are under way on the federal level to evaluate this situation and work toward harmonization, but I am not certain about the degree to which states are involved. For some time now there have been efforts among several federal agencies to reach consensus on the assumptions employed in hazard assessment. An example of this relates to the Food Safety Initiative, which involves USDA, FDA, and EPA. It is apparent that the three agencies often have distinct philosophies and differences of opinion on how hazard assessment should be conducted. These differences do not necessarily serve the purpose well. Yesterday, another example was alluded to that acknowledged differences in opinions among agencies. I assume this was in reference to dioxin, a chemical for which there are not only differing U.S. federal agency approaches to hazard assessment, but also differences from and between governments internationally. A wide range of opinion also exists regarding the potential risk from exposure to dioxin. We also would find differences of opinion if we took a different chemical and asked these agencies to conduct risk assessments. I think that in the future, access to and sharing of hazard assessment data and additional conferences like this will become increasingly important. Let's focus on building a consensus on how best to evaluate and use the data and move forward from there.

There have been efforts among several federal agencies to reach consensus on the assumptions employed in hazard assessment.

Redundancy in the generation and storing of information by federal and state governments is discussed.

EPA is not the only agency that does risk assessment. Virtually

every federal agency that has some interest in the environment (in the broadest sense), does some risk assessment, either from the human health or the environmental aspect.

Information Resources in State Regulatory Agencies—A California Perspective

Stephen M. DiZio, California Environmental Protection Agency

Various state regulatory agencies have expressed a need for networking with information gatherers/researchers to produce a concise compilation of primary information so that the basis for regulatory standards can be scientifically referenced. California has instituted several programs to retrieve primary information, generate primary information through research, and generate unique regulatory standards by integrating the primary literature and the products of research. This paper describes these programs.

Introduction

Our speakers today from Massachusetts, New Jersey, Tennessee, Illinois, Louisiana, and Connecticut have touched on a number of recurring themes. These consist of a reliance on federal sources, such as the Oak Ridge National Laboratory; the Agency for Toxic Substances and Disease Registry (ATSDR); and the U.S. Environmental Protection Agency (EPA), especially the Integrated Risk Information System (IRIS) as available electronically through the National Library of Medicine, for risk assessment information. The primary needs identified are for networking with those information gatherers/researchers to produce a concise compilation of primary information so that the basis for regulatory standards can be scientifically referenced.

The State of California shares these needs, and has instituted several programs to retrieve primary information, generate primary information through research, and generate unique regulatory standards by integrating the primary literature and the products of research.

Retrieval of Primary Information

The State of California has instituted several programs to retrieve primary information, generate primary information through research, and generate unique regulatory standards by integrating the primary literature and the products of research.

Primary information, meaning that available in the literature on the toxicity, environmental fate, and exposure assessment of chemicals is essential to the regulatory decision-making process utilized by the California Department of Health Services (DHS), Department of Toxic Substances Control (DTSC), Department of Pesticide Regulation (DPR), Office of Environmental Health Hazard Assessment (OEHHA), and Office of Emergency Services. This information is made available to these groups through several sources, including the libraries of the University of California (UC), on-line electronic data services, and the National Laboratories managed by UC.

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1. Library services

Information resources made available through the UC libraries are funded by a large contract with the UC Berkeley public health library. Historically, the DHS has maintained this funding, although with the recent

creation of the California Environmental Protection Agency (Cal EPA) the various groups within Cal EPA such as OEHHA, DTSC, and DPR have assumed authority over this funding and have centralized management of the contract within OEHHA. The contract provides access to all the information resources within the entire UC system; thus, literature unavailable at Berkeley is easily obtained through other campuses, primarily those at UC Davis and UC Los Angeles (UCLA). This vehicle has provided the primary source of published literature for state scientists in the development of regulatory standards.

Recently, specialty libraries at some of the UC campuses were contracted separately for literature search and retrieval services because of the unique capabilities of a specialty library to quickly and concisely summarize the relevant information within a particular field. One important example has been the Environmental Toxicology Information Center within the Environmental Toxicology Department at UC Davis. This group provided valuable service to DTSC and DPR. The library and its personnel are dedicated to storage and retrieval of textbooks, journals, and articles on the toxicity, fate and transport, and environmental exposure of pesticides and other major environmental pollutants. Consequently, the library may serve as an essential arm of the DTSC and DPR when this information is needed quickly for regulatory decision making. During the Loma Prieta earthquake of 1989, the library installed dedicated telephone equipment for quick data retrieval and communication, whereas San Francisco bay area facilities were handicapped as a result of disruptions in essential services caused by the temblor.

Government libraries, particularly the EPA Region IX library in San Francisco, also serve as sources of primary information not easily obtainable through the academic system. In particular, the DTSC has made extensive use of this facility for examination and retrieval of various EPA Fact Sheets dealing with a wide range of issues such as the proposal of new maximum contaminant levels (MCLs) or the permitting of landfills.

Speciality libraries of the UC campuses are contracted separately for search and retrieval because of the unique capabilities of a specialty library to quickly and concisely summarize the relevant information within a particular field.

2. Electronic data retrieval

Many state agencies, particularly the Office of Emergency Services and DTSC maintain sizeable contracts with services such as Lockheed Information Systems (DIALOG) and the National Library of Medicine (MEDLARS) for quick access to literature abstracts and on-line databases, particularly IRIS and the Hazardous Substances Data Bank (HSDB) as available through TOXNET. In addition, on-line bulletin board systems, such as those operated by the EPA Office of Solid Waste and Emergency Response are often utilized as supplemental sources of information, particularly for U.S. government publications, which are often not stored in the UC library system.

Use of the information available on line is varied.

Use of the information available on-line is varied. In emergencies such as evaluation of public health hazard of a rail spill, the availability of HSDB through a modem contained on a portable computer has made quick access

to relevant information possible for DTSC and DHS. In regulatory standards development, literature searches form the basis for the assessment of both resource allocation and time requirements for project completion by DPR and DTSC. For research, data gaps in the available literature are first identified by on-line searches so that project priorities may be developed. Thus, California governmental agencies use a wide range of electronic information resources to answer specific needs relating to risks from chemical exposure.

3. National laboratories

Primary information retrieval from the national laboratories managed by UC, Lawrence Berkeley Laboratory (LBL), and Lawrence Livermore National Laboratory (LLNL), is necessary because of their respective systems of excellent in-house publications. Projects conducted for various governmental agencies, as well as original research conducted by each national laboratory, are often first published in-house prior to publication in the public literature. Therefore, for state agencies to maintain state-of-the-art knowledge of the fields of exposure assessment and environmental risk assessment, access to these publications through contract or collaborative effort is essential. Two examples of this, by no means unique, are the models of showering exposure and probabilistic uncertainty analysis conducted by Thomas McKone and Kenneth Bogen of LLNL, which were first available as LLNL UCRL publications. Advance knowledge of these efforts were necessary for California to develop modern drinking water standards as well as to make responsible regulatory decisions in cases where uncertainties existed in public exposure estimates.

Generation of Information through Research

Both the DTSC and the DHS have funded original research designed to provide information necessary for the development of regulatory guidance, regulatory standards, and risk-management decision making. This research was conducted by major contracts between DHS and DTSC with the Regents of UC, allowing access to all campuses within the UC system as well as the national laboratories. Some of the projects are described below.

Both the DTSC and the DHS have funded original research designed to provide information necessary for the development of regulatory guidance, regulatory standards, and risk-management decision making.

1. Research on assessment of exposure resulting from showering

The Environmental Sciences Division of LLNL conducted research in a home purchased by the laboratory on the showering exposure to trichloroethylene (TCE). This project was funded by DTSC. Bathroom plumbing was modified to add measured amounts of TCE to shower water, and analyses were made of the release of TCE into various bathroom "compartments" (e.g., shower walls, wet towels, and bathroom air) so that modeling of inhalation exposure could be developed from information gathered in an actual home. In addition, the dermal permeability of TCE at environmentally relevant concentrations in water (parts-per-million levels) was measured in laboratory animals under controlled conditions to

The Environmental Sciences Division of LLNL conducted research in a home purchased by the laboratory on the showering exposure to trichloroethylene (TCE).

better estimate dermal exposures during swimming or showering.

2. Research on particle inhalation by children

UC Irvine was funded to provide experimental data on the inhalation of fugitive dust particles by humans by studying both the nose as a selective sampling device as well as the influence of body size. Wind-tunnel experiments with particles delivered in a laminar flow were designed, and mannequins with laser devices embedded in the noses were used to identify subsets of populations exposed to dust particles dispersed from hazardous waste sites by wind erosion. Children, because of small body size, were identified as the group with the greatest exposure to inhalable particles. This project was funded by DTSC.

3. Research on dermal absorption of soil contaminants

The Department of Dermatology at UC San Francisco was funded by DTSC to provide information on the dermal absorption of contaminants from soil. *In vitro* experiments were conducted on selected chemical groups, including pesticides (chlordane, DDT, and pentachlorophenol), metals (cadmium and arsenic), and other environmental contaminants (e.g., benzo-*a*-pyrene) to evaluate their penetration through human skin. Some of these compounds were also tested *in vivo* in validation experiments in which dermal absorption was measured from soil applied to the skin of rhesus monkeys. This research has been singularly fruitful, with regulatory impact where soil exposure and cleanup is at issue.

4. Research on exposure modelling

LLNL was requested to construct theoretical multipathway risk assessment modeling experiments to both integrate original experimental results and to provide an evaluation of secondary source contributions to exposure and risk. The resulting effort has integrated experimental results, critical evaluation and selection of relevant physicochemical parameters, and professional peer-reviewed modeling into an unique multipathway tool designed to provide remedial objectives for selected environmental media, such as soil. Its use will be described in the following item.

5. Research on nonaqueous phase liquid transport in vadose zone soil

LBL has been funded by DTSC to provide original research on transport of nonaqueous phase liquids (NAPLs) through soil to the water table. This project, now in it's third year, will be used to generate the information needed for DTSC guidance on the evaluation of the movement of NAPLs at hazardous waste sites or facilities.

Generation of Guidance and Standards

Guidance for exposure assessment and risk assessment, regulatory standards for acceptable pesticide residues on crops, and the development of regulatory drinking water standards are but some of the uses that California agencies made of information derived from information services and that gathered through original research. The following

The Department of Dermatology at UC San Francisco was funded by DTSC to provide information on the dermal absorption of contaminants from soil.

LBL has been funded by DTSC to provide original research on transport of nonaqueous phase liquids (NAPLs) through soil to the water table.

examples are by no means all-inclusive of the use of these services by California agencies.

1. Development of California drinking water standards

The state legislature authorized DHS to develop 36 California drinking water standards (MCLs) to supplement those being developed by the federal government. Chemical risk assessments, used as the basis for the selection of MCLs by the Sanitary Engineering Branch of the DHS, were written by various groups within the UC campus system, primarily UC Davis, and the LLNL. These documents were subjected to national peer review and were used to identify a range of scientifically acceptable concentrations for acceptable risk or hazard of the individual agent.

2. Development of technical guidance and standards

Technical guidance was deemed necessary for the implementation of the DTSC Integrated Site Mitigation process, with key guidance promulgated as regulation. Regulation development was restricted to the department. Guidance document development, in terms of exposure modeling, exposure pathway selection, use of multimedia models in a back-calculation of soil remediation levels as mentioned in the preceding, and probabilistic analysis of uncertainty was contracted by DTSC to LLNL. These were designed to integrate the information resources developed and utilized by all state agencies with those research projects mentioned in the preceding, and provide workable tools for environmental remediation to be used by both the public and private sectors.

Conclusions: Future Needs

One of the goals of this conference was to identify current and future needs in the field of information resources. From the state perspective, several major items were identified as necessary and appropriate goals for those supplying information resources to the state agencies.

The State legislature authorized DHS to develop 36 California water standards to supplement those being developed by the federal government.

1. Better information exchange among states

Several of the speakers expressed the desire for some form of directory and formal information exchange system so that unique resources developed by an agency in one state would be accessible to agencies in other states. The existence or development of air, water, and soil criteria has been mentioned by several state representatives, provoking great interest from their counterparts in other state and federal agencies.

Currently, the most effective tool for this sort of exchange has been the telephone. However, as this resource database grows, a more systematic and readily accessible vehicle will be necessary to achieve maximum utilization of these products and to avoid unnecessary duplication of effort. The experience in California has been that, even within a state, the growth of various agencies with risk assessment responsibilities has resulted in a loss of effective communication, resulting in duplication of effort.

Technical guidance was deemed necessary for the implementation of the DTSC Integrated Site Mitigation process, with key guidance promulgated as regulation.

2. Better information exchange about local problems that occur nationwide

Certain items requiring risk assessment support occur nationally but are not systematically addressed by either the federal RCRA or CERCLA programs. One such case that immediately comes to mind is that of the manufactured gas facilities. Before natural gas was widely distributed, coal and diesel gassification plants flourished in many urban settings. The buried waste derived from the operation of these plants occurs from coast to coast across the United States. Although many of the problems associated with these facilities are similar they are dealt with at state and local levels. Consequently, there is a need for better exchange of information between the states about how risks are assessed and managed at these facilities. An archival system for such information would improve the efficient handling of these and similar problems.

Certain items requiring risk assessment support occur but are not systematically addressed by either the federal RCRA or CERCLA programs.

3. Epidemiological support

Dr. David Brown of the Connecticut Department of Health spoke of the critical need for exchange between states about how rapid, end-point specific information is used to arrive at a decision when human health risk is immediately apparent. His experience consulting with his counterparts in California illustrates the need for a more systematic, possibly centralized system whereby epidemiologists and other health professionals can be identified and information sources can be quickly accessed when problems arise.

How Information Resources Are Used by State Agencies in Risk Assessment Applications—Illinois

Clark S. Olson, Illinois Environmental Protection Agency

The Environmental Protection Agency of the State of Illinois (Illinois EPA) has programs in water, air, and land pollution and water supplies paralleling those of the U.S. Environmental Protection Agency (EPA). The organization is part of a tripartite arrangement in which the Pollution Control Board is the judicial arm, the Department of Energy and Natural Resources is the research arm, and the Illinois EPA is the enforcement arm. Other state agencies are also concerned with various aspects of the environment and may do risk assessments for chemicals. Although there are various risk assessment activities, both formal and informal, in our agency and in others, this paper will discuss only recent initiatives in water quality criteria.

Water quality criteria are similar to water quality standards for acceptable environmental levels of substances, except that the legal force is not as great. Standards include consideration of economic, technical, and social impact of the regulation, whereas criteria are intended to be completely "scientific." In other words, standards can contain an element of risk management, whereas criterion determination is more purely risk assessment. Basically, we can calculate a criterion and implement it ad hoc whereas the Pollution Control Board sets standards that apply more uniformly and widely. Our criteria are calculated for setting effluent limits, for cleanup levels in spills and as general goals for nonpoint pollution.

In this new initiative of controlling "toxics" in water, the states were given a choice of adopting whatever national numbers were available, adopting a procedure for obtaining numbers, or a combination of the two. Illinois adopted the approach of setting a procedure and calculating numbers as needed. If the number is used in a legal document, which will most likely be the permit, the public can challenge the number.

Our criteria are calculated for setting effluent limits, for cleanup levels in spills, and as general goals for nonpoint pollution.

We have a methodology for calculating criteria for acute and chronic effects in aquatic life and to protect wildlife and human health. The latter criteria are for chronic exposure. The procedure for calculating criteria for aquatic life is much more explicit and detailed than that for calculating criteria for wildlife and human health. Criteria, or at least criteria documents, have been published for the so-called "priority pollutants" and for a small number of other substances. However, no wildlife criteria are included in that program.

We have a methodology for calculating criteria for acute and chronic effects in aquatic life and to protect wildlife and human health.

We are using the new regulations to calculate criteria for aquatic life. We are not sure when or how criteria for wildlife or human health will be implemented, but some of the same principles and concerns related to

calculating criteria for aquatic life will apply. However, it is evident that the sources of data and kinds of end points will be different.

In calculating criteria, the immediate information needs are for simple end points for acute and chronic effects — LC_{50} and no-effect levels. In addition, we consider information on bioconcentration, log P, quantitative structure activity relationship (QSAR) studies, sublethal effects, ecosystem level effects, metabolism, and environmental fate.

There are several functions involved in developing a criterion: (1) finding and identifying the necessary data; (2) getting the data, preferably from the original document; (3) selecting and evaluating the data to make the calculation according to set procedures; and (4) considering any other kinds of information necessary to make a final evaluation or validation of the numbers.

To go about these various tasks, our physical and personnel resources include a technical library within the agency that is supervised by an experienced reference librarian. The library staff is capable of searching in National Library of Medicine (NLM) and Lockheed data bases. The library contains 18,000 books, 350 journals, and 25,000 other documents and has interlibrary loan services. We also have a separate group of toxicology and environmental chemistry specialists, one of whom is capable of searching EPA data bases. Also available in Springfield, where we are located, are the main state library and two university libraries.

With regard to the above items (1) and (2), search and retrieval, two principles are written into our regulations. One is that the literature search should be complete, and the other that we should try to get the original document.

Several functions are involved in developing a criterion.

The first task is of course impossible, but we interpret it to mean that we should look beyond the relevant EPA data bases. In contrast, I think there are agencies and consultants that would consider a search on AQUIRE to be sufficient, for instance, in doing a criterion calculation for aquatic life. We would like to define or outline what might be considered an adequate literature search, but that probably will not be possible for some time.

The most likely starting place for us is the water quality criteria documents published by EPA, along with some water quality "advisories" for some additional chemicals. The reason for starting with the priority pollutant water quality criteria documents is that our chemists are mainly looking for "priority pollutants." We need to search beyond these documents because they are generally out of date, because we need to get data relevant to our state, and because in many cases a calculated criterion is not actually given anyway. Also, we have found a few instances in which data were not included. Second, we often will do a search on AQUIRE. We may get to the point at which we might consider this obligatory. Another source is the June literature review issue of the *Journal of the Water Pollution Control Federation*. This resource sometimes gives the actual toxicity

Two principles are written into our regulations. One is that the literature search should be complete; the other is that we should try to get the original document.

data and at least has bibliographic information. Finally, we think that manual searching is still necessary; that is, checking through the bibliographies of more recent papers to see if they contain any references to earlier papers not yet identified.

Computerized data bases offer many advantages but may also have some drawbacks if they are used uncritically. The main advantage is that they are a fast way of identifying all references, including "gray," foreign, and older literature, original copies of which are hard to get. However, we are not sure whether we can use these sources anyway. In addition, computerized data bases may contain some data evaluation to assist with functions (3) and (4) of developing criteria, and an evaluated data base may present the experimental details of toxicity tests in a systematic way. The difficulties with computerized data bases are redundancy (i.e., data may be incorporated more than once because it was published in more than one place), incompleteness, inaccuracy, and currentness.

To adhere to the second principle built into our regulations, that the original document should be obtained and used, takes time and costs money for interlibrary services when we do not have the original document in our library. It also means that we are going to have to build up a reprint file, but the library may be able to do that.

In summary, our efforts with calculation of aquatic criteria have presented some problems, but the challenge of selecting data sources and mathematical models with which to set wildlife and human criteria appears to be even more daunting for the future.

Computerized databases offer many advantages but may also have some drawbacks if they are used uncritically.

Information Resources: How They Are Utilized by Louisiana

Suzanne Gardner, Louisiana Department of Environmental Quality

Louisiana, now in a developmental stage of policy and planning, has completed a project aimed at reducing hazardous releases of air toxics in the state. The state is also conducting a Comparative Risk Project and is using risk assessment practices to develop its water quality standards.

In developing an air toxic list, Louisiana incorporated four major criteria into the ranking: emission levels, human health effects, potential population exposure, and persistence or accumulation in the environment. For the human health effects criterion, data for each substance was gathered from numerous sources, although the Integrated Risk Information System (IRIS) database was used as a primary source for toxicological information.

Following guidelines established by the Environmental Protection Agency (EPA), the Office of Water Resources, Water Pollution Control Division, has developed numerical criteria for human health protection based on risk assessment procedures in the 1989 Water Quality Standards Revision. Currently over 30 toxic substances have risk-based criteria for the protection of human health in the standards. Numerical criteria were calculated for carcinogenic substances having an EPA Classification of A, B1, B2, or C. Cancer class designations along with cancer potency slopes and reference doses were extracted from the IRIS database, with the exception of those chemicals that had not been assessed in IRIS as of December 1, 1988. The parameters necessary for calculating human health criteria for the missing chemicals were taken from 1980, 1984, and 1985 ambient water quality criteria documents; data on bioconcentration factors were included.

Currently, Louisiana is working on a Comparative Risk Project, a ranking of the environmental issues in the state relative to potential risk to the public, which is the basis for a widespread 1991 public outreach effort.

The Louisiana Department of Environmental Quality (LaDEQ), utilized information resources as a vital tool in developing planning strategy.

The department recently completed a project aimed at ranking air toxics based on toxicological data. The state used risk assessment analyses to develop water quality criteria. Currently, the Office of Policy Analysis and Planning is conducting the Louisiana Comparative Risk Project, a project that compares risk across various environmental issues. This labor intensive project requires the use of information resources over a broad spectrum of issues.

In an attempt to reduce statewide air emissions, Louisiana passed the Comprehensive Toxic Air Pollution Control Program, Act 184, in June of 1989. A list of not more than 100 toxic air pollutants was to be regulated in accordance with Act 184. To rank these pollutant compounds, several information resources were needed. Various criteria have been used by other states. Most use the pounds discharged and the potential population exposed. Louisiana established four criteria for ranking air pollutants: amount discharged, potential population exposed, human health effects, and persistence in the environment.

The first step was to identify the chemicals to be included. The Superfund Amendment Reauthorization Act (SARA), Title III, provided the basis for the list. Of a total of 319 chemicals, 178 were reported to be emitted into the air in Louisiana.

Louisiana uses a variety of information resources in developing environmental planning strategies.

Calculations of the pounds discharged were based on the 1987 SARA Toxic Chemical Release Inventory Database. The database consists of mandated company reports of intentional and nonintentional releases. Point and nonpoint emissions were totaled for each chemical emitted in Louisiana.

Calculations of potential population exposure were based on U.S. Census track data, utilized with the help of the geographic information service laboratory at Louisiana State University Campus Laboratory. A 10-km radius for each emitting facility was established and the Geographical Information System (GIS) estimated population within each 10-km area. The assumption was made that the population within each designated area was evenly distributed. For human health effects, the Integrated Risk Information System (IRIS) database was used.

IRIS was selected for its risk assessment and risk management information. The qualitative and quantitative risk assessments served as guidelines to evaluate the potential hazard of chemicals. Quantitative risk assessment included potency factors, unit risk, and air concentrations at designated risk levels. For accumulation and persistence in the environment, the information was harder to find. Data needed included atmospheric half-lives, evaporation rates, vapor pressures, and reaction rates. Missing toxicological data were calculated using reference doses (RfDs), where applicable, taking into account uncertainty factors. Inhalation studies were given preference over other studies.

One of the problems was the vast amount of information needed for each chemical. For several chemicals, such as benzene, abundance of toxicological data was found, whereas in other cases, such as picric acid, very little information was found.

Once the data were collected, a ranking for each criteria was performed by designating a positive integer for each criteria: the higher the integer, the higher the hazard. By this process, each chemical was assigned a set of numbers corresponding to the severity of each criteria. These numbers were then loaded into a Hasse computer-ranking program, developed by Dr. Ephram Helfin of Canada, which establishes binary relationships between chemicals by comparing one data point with another. The result is displayed graphically as diagrams that resemble branch-like structures, much like a genealogical tree.

In developing the water quality standards, the Office of Water Quality Resources, Water Pollution Control Division, developed human health protection standards based on risk assessment analyses. Risk-based values have been established for over 30 toxic substances. Numerical criteria were developed for those substances with an EPA carcinogenic classification of A, B1, B2, or C. Cancer potency slopes and RfDs were taken from IRIS. Data unavailable from these sources, including bioconcentration factors, were taken from 1980, 1984, and 1985 ambient air and water criteria documents. A number of assumptions had to be made: the use of 2 L for water consumption, the use of 70 kg

Louisiana's comprehensive Toxic Air Pollution Control Program utilizes IRIS for its risk assessment and risk management information.

In developing water quality standards, the Office of Water Quality Resources, Water Pollution Control Division, developed human health protection standards based on risk assessment analyses.

for the average adult body weight, and a one-in-a-million health risk for carcinogens. An incidental ingestion rate (89 mL/day) was calculated with the help of the Department of Health and Hospitals.

In our criteria, the water quality standard for each chemical is proportional to the product of the risk level and the average adult body weight, divided by the slope factor, and the ingestion rate, the average water consumption, the bioconcentration factor, and a fish consumption rate (0.02 kg/day).

$$\frac{\textit{Average adult body weight} \times \textit{Selected risk level}}{\textit{Slope factor}\,[\textit{Avg. water consumption} + \textit{Incidental ingestion rate} + \textit{Fish consumption rate}\,(\textit{Unit conversion factor})(\textit{BCF})]}$$

For noncarcinogens, RfDs were substituted for the risk levels of 10^{-6}. We utilized this calculation for both public and nonpublic water supplies.

Currently, LaDEQ is working on the Louisiana Comparative Risk Project, which ranks the environmental issues in Louisiana relative to the risk to the public. This follows a similar 1987 investigation by EPA called "Unfinished Business," a comparative assessment of an environmental issue. For each issue, scenarios will be developed that represent the importance and magnitude of each issue. Each issue will be put through three levels of analysis: health effects, ecological effects, and welfare effects. The health effects assessment will assess the health risk associated with each issue. The assessment of ecological effects will include effects on the economy. Welfare effects include those effects that affect quality of life. The second level of analysis will be to rank the problem areas within each effect category. The third level of analysis will be to rank the issues across effect categories.

This process includes multidisciplinary involvement across various agencies around our state. Information resources and data will be collected statewide for this project. Louisiana is one of the few states currently to start a comparative risk project. The comparative risk project will redirect up to 30% of state monies, so each agency has a stake in this project.

LaDEQ is working on the Louisiana Comparative Risk Project, which ranks the environmental issues in Louisiana relative to risk to the public.

The health effects assessment will assess the health risk associated with each issue. The ecological effects will include effects on the economy. Welfare effects include those that affect quality of life.

Access and Use of Information Resources by Massachusetts

Carol Rowan West, Massachusetts Department of Environmental Protection

This paper describes the way in which the Massachusetts Department of Environmental Protection uses risk assessment to implement the state's environmental laws. It focuses on the Office of Research and Standards, which was created to provide information on adverse health effects of environmental contaminants, to recommend exposure levels, and to direct and manage research programs.

Introduction

The Massachusetts Department of Environmental Protection (DEP) is the state agency charged with protecting and enhancing the quality of the Commonwealth's natural resources—its air, water, and land—to provide for the health, safety, welfare, and enjoyment of the public and the protection of private property.

DEP fulfills its mission by implementing a number of environmental laws. The laws passed and enforced to date include

- Clean Air Act (state and federal)
- Clean Water Act (state and federal)
- Safe Drinking Water Act (state and federal)
- State Solid Waste Regulatory Law (21H)
- State Hazardous Waste Regulatory Law (21C)
- Federal Resource Conservation and Recovery Act
- Superfund Law (state and federal)
- State Right to Know Law
- Wetlands Protection Act (state)
- Wetlands Restriction Act (state)
- Tidelands Law (Chapter 91) (state)
- Low Level Radioactive Waste Law (state)
- Toxic Use Reduction Act (state)

The DEP fulfills its mission by implementing a number of environmental laws.

Some of these laws are established to protect a particular resource such as air and drinking water, whereas others are aimed at solving environmental problems, such as solid and hazardous waste disposal. The common characteristic is the focus on toxic chemicals—to prevent environmental pollution and adverse impacts on public health and the environment.

Some of these laws are established to protect a particular resource such as air and drinking water, whereas others are aimed at solving environmental problems, such as solid and hazardous waste disposal.

The Office of Research and Standards (ORS) was created in 1980 to serve all DEP programs by providing information on adverse health effects of environmental contaminants, to recommend exposure levels protective of public health and the environment, and to direct and manage the departmental research programs that serve as the technical

basis for appropriate policy and program development. ORS currently has 12 full-time toxicologists and environmental scientists on staff.

To achieve its mission within DEP, ORS has many duties and performs many functions. The major areas of responsibility of ORS are shown in Table 1.

Although the ability of ORS to conduct all of these activities effectively depends on many factors, the timely access of quality and useful information is among the most important requirements.

General Description of Methods Used by ORS

ORS conducts risk assessment work for the DEP programs by using the four step process outlined by the National Academy of Science (1983). In addition, ORS participates in the DEP risk management decisions by providing not only the results, but also the description of uncertainty inherent in the risk assessment work. Risk management decisions may consider technical feasibility and economic and social impacts along with risk assessment results, depending on the particular statute. After risk management decisions are made, DEP next develops and implements a risk communication plan, generally under a team approach, in which staff from the particular program, the public affairs office, and ORS all participate. Here, ORS assists the DEP to involve the public in understanding the risk assessment process and results.

ORS accesses information for its risk assessment work in a variety of ways, as presented in Table 2.

Table 1. Major responsibilities of the Office of Research and Standards (ORS)

- Develop risk assessment protocols to assess impacts of toxic chemicals
- Establish standards and health-based guidelines for chemicals in air, water, and soil
- Conduct hazardous waste site risk characterization work
- Evaluate environmental monitoring data and advise DEP on public health protection
- Develop Health Hazard Indices for chemicals
- Recommend listing of chemicals for inclusion in regulatory programs
- Maintain toxicity databases
- Provide technical support on enforcement cases
- Direct and manage environmental research

Manual searches are very effective for ORS because the office is located in the Boston area, which is well-endowed with medical and research institutions. Access to these numerous libraries allows ORS to obtain virtually any journal or reference material locally or through interlibrary loan systems. ORS has also been provided an annual budget to maintain an in-house library. Although ORS manual searches are very productive, the time necessary to conduct them can have drawbacks in situations in which immediate response is needed.

Another way ORS obtains information is through on-line computer access, the U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), miscellaneous technical bulletin boards, and the ORS-developed on-line reference database. Use of these systems is expedient but is lim-

Table 2. ORS access to information

- Manual searches
- On-line access
- Reliance on others — EPA, ORNL, other state agencies

ited by the number of chemicals for which information is maintained in these systems relative to the ORS needs. ORS is limited by lack of on-line information resources, and so must rely on another means of information access—consultation with others, most notably the EPA, Oak Ridge National Laboratory (ORNL), and other state agencies. In many instances ORS received information transfer assistance from others, including the EPA, Air Risk Information Support Center (Air RISC), Office of Health and Environmental Assessment, the Federal-State Toxicology and Regulatory Alliance Committee (FSTRAC), Office of Pesticides and Toxics Substances, and ORNL. In these cases, information access is typically faster than manual searches but slower than on-line systems.

ORS utilizes a number of information resources in conducting risk assessments. Key resources are shown in Table 3.

Table 3. Key data sources used by the Office of Research and Standards

1. Hazard identification
   - IRIS
   - ATSDR Toxicity Profiles
   - EPA Criteria and Health Assessment Documents
   - HEAST
   - GENE-TOX Database
   - IARC
   - NTP/NCI bioassays
   - NIOSH, ACGIH, OSHA occupational literature
   - NATICH
   - EPA One-Liners
   - FDA Tolerance Limits/Advisories
2. Dose response assessment
   - IRIS
   - HEAST
   - Occupational literature
   - Primary literature
3. Exposure assessment
   - EPA guidelines for exposure assessment
   - ORS default values
   - Risk characterization and uncertainty analysis
   - All of the above

Practical Problems With Information Access

ORS has two types of problems with access and use of information resources in assessing health risks from chemical exposure: one is accessibility, the other is a technical problem.

Accessibility problems arise because of resource constraints. For example, the agency does not have a professional librarian to obtain all information that is available, and staff time for information access is limited. ORS' direct access to on-line systems is very limited. ORS relies heavily on other agencies for access to information, which has worked fairly well, but the office's needs cannot always be met. In addition, because of the nature of the public health protection work that we conduct, there are instances in which ORS results are needed immediately. In such cases, information gathering activities are limited by deadlines, hence information that could be useful may not be obtained.

With regard to technical problems, it is evident that access to information resources does not translate directly into the ability to provide all of the answers to environmental health problems. Typical examples of risk assessment issues that result from technical data limitations are shown in Table 4.

Table 4. Technical problems

- Evaluating less than lifetime exposure
- Lack of toxicity testing of chemicals
- Standard toxicity testing protocols not followed
- Route of administration
- High to low dose extrapolations
- Chemical form, specification
- Appropriate animal model for humans
- Lack of human toxicity data
- Uncertainty factors

Conclusions

To conduct risk assessments for the protection of public health from environmental contaminants, access to information should be readily available, reliable, able to meet time constraints, and affordable. Improvements in risk assessment work will be achieved only when more complete data on chemicals can be generated (including information on adverse health effects, routes of administration, and duration of exposure) and better methods (including appropriate animal models and extrapolation to humans) can be developed.

These ideal conditions are not now within our reach, but professionals involved in this field from state, federal, and international agencies, as well as private institutions should work together to achieve what is possible. The importance of this work in terms of lives saved and human suffering reduced is worthy of such an effort.

These ideal conditions are not now within our reach, but professionals involved in this field from state, federal, and international agencies, as well as private institutions should work together to achieve what is possible.

References

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Information Resources Used in Health Risk Assessment by the New Jersey Department of Environmental Protection

Gloria B. Post, Maria Baratta, Sharon Wolfson, and Leslie McGeorge,
New Jersey Department of Environmental Protection

The New Jersey Department of Environmental Protection's responsibilities related to health-based risk assessment are described, including its research projects and its development of health based compound specific standards and guidance levels. The resources used by the agency to support health risk assessment work are outlined.

The New Jersey Department of Environmental Protection (NJDEP) performs a number of functions relating to health risk assessment which require information resources. NJDEP is unique in including a Division of Science and Research (DSR), which conducts research projects and provides other types of technical support to the department. A major strength of DSR is in toxicology and assessment of health risks. Activities in these areas include developing and managing research projects; developing compound-specific standards and guidance levels; site-specific evaluations; replies to citizen's inquiries; and providing technical assistance to other NJDEP Divisions.

NJDEP has its own Information Resource Center (IRC), which is part of DSR and is available to the entire department. The IRC is a technical library that has reference materials, technical journals, government documents, books, and data base searching capabilities; a staff of five operates the center. Information resources used in assessing human health risks include data bases such as the National Library of Medicine (NLM) files (specifically HSDB and TOXLINE), IRIS, and DIALOG, as well as information retrieval, interlibrary loans, and access to federal government documents. Additionally, DSR is cosponsoring, along with EPA and the California Department of Health Services, the development of Risk Assistant, a microcomputer-based software system that will be used by individuals with limited expertise in risk assessment to assess health risks at hazardous waste sites. Risk Assistant includes databases on toxicity, regulatory standards, chemical properties, and analytical limits and is capable of estimating exposures and risk levels. These capabilities allow NJDEP to perform original compound-specific and site-specific risk assessments and to provide the technical basis for research activities.

DSR's Information Resource Center provides access to technical information required for risk assessments.

These capabilities allow NJDEP to perform original compound-specific and site-specific risk assessments.

NJDEP is a large agency that has about 4000 employees. As shown in the departmental organizational chart (Fig. 1), NJDEP consists of a number of

divisions and is organized generally along media-specific lines. Many of the divisions with responsibilities relating to particular environmental media perform or use human health–based risk assessment to some extent. For example, the Bureau of Environmental Evaluation and Risk Assessment within the Division of Hazardous Site Mitigation reviews risk assessments of contaminated sites that have been submitted to NJDEP; the Bureau of Air Quality Planning and Evaluation within the Division of Environmental Quality uses risk assessments in developing permits for certain types of air emissions; and the Bureau of Safe Drinking Water in the Division of Water Resources relies on risk assessment information to provide guidance in situations of contaminated potable water.

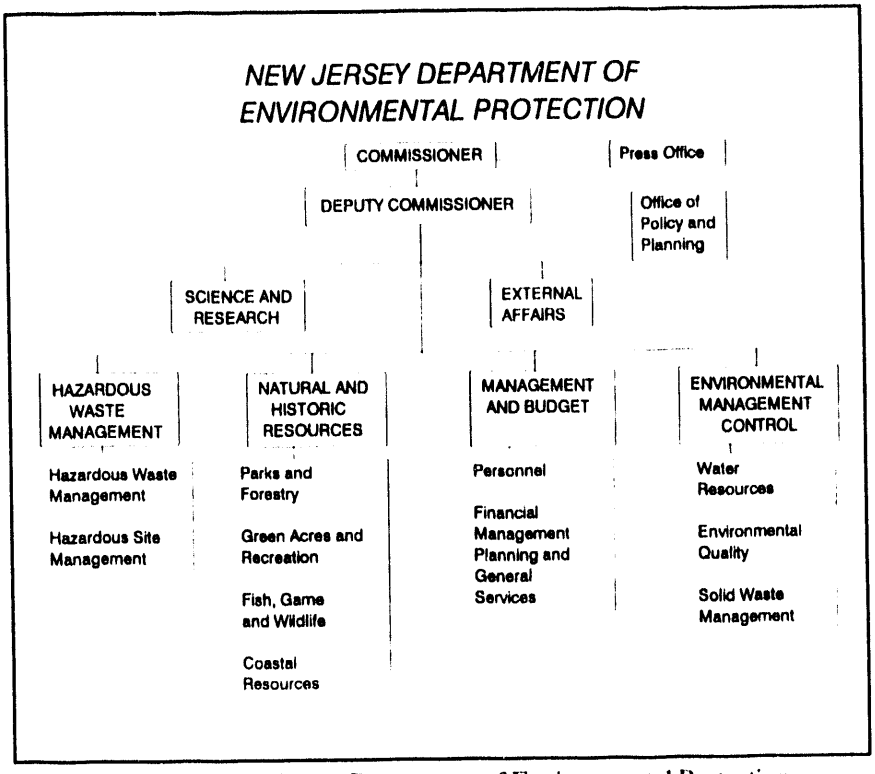

Fig. 1. New Jersey Department of Environmental Protection.

NJDEP is unique in that it includes the Division of Science and Research (DSR), which reports to the Commissioner's Office. DSR conducts research projects and provides other types of technical support to NJDEP, particularly in addressing cross-media issues or nonroutine situations. DSR is responsible for overall coordination of the risk assessment activities of NJDEP and sponsors the Interagency Risk Assessment Committee (IRAC), which consists of staff from various divisions of NJDEP and the New Jersey Department of Health who are involved with risk assessment. IRAC meets regularly to hear invited speakers present topics of general interest and to discuss risk assessment issues.

DSR was originally founded in 1976 as the Program in Environmental Cancer and Toxic Substances to evaluate the potential carcinogenicity of environmental contaminants. Although it has branched out into many other areas since that time, its primary emphasis remains that of assessing the extent of exposure and the health effects of environmental contaminants. In 1986, the Office of Environmental Health Assessment (OEHA) was implemented within DSR through a governor's initiative. OEHA's mandate is to provide expertise in the areas of risk assessment, risk communication, and risk reduction to NJDEP.

DSR consists of approximately 40 professional staff, with expertise in many fields including toxicology, genetic toxicology, public health, environmental science, physics, geology, chemistry, aquatic biology, geography,

Areas of research include toxicology, exposure assessment, epidemiology, biological monitoring, and risk assessment modeling.

communication, and library science. The organizational structure of DSR is shown in Fig. 2. Within DSR, the Risk Assessment Unit and the Environmental Exposure Unit are the major groups that perform risk assessment–related work.

DSR has sponsored and/or conducted a number of research projects relating to human health risk assessment. Areas of research include toxicology, exposure assessment, epidemiology, biological monitoring, and risk assessment modeling. The research projects are designed to provide specific information required by NJDEP to address New Jersey environmental problems and to contribute to the general knowledge in the field.

DSR research projects include the following: bioavailability studies of dioxin and chromium from contaminated soils; determination of pesticide residues in crops grown or sold in New Jersey and risk assessment based on these levels; total human exposure study of benzo[*a*]pyrene, including measurement of benzo[*a*]pyrene-DNA adducts in blood samples from subjects; total exposure and biological monitoring of subjects living on chromium-contaminated sites; exposure assessment and neurobehavioral effects of orchard farmers with chronic pesticide exposure; pulmonary carcinogenicity of chromium-contaminated soil; toxic interactions of two chlorinated drinking water contaminants; and use of quantitative structure activity relationships to predict carcinogenicity of trihalomethanes and related compounds.

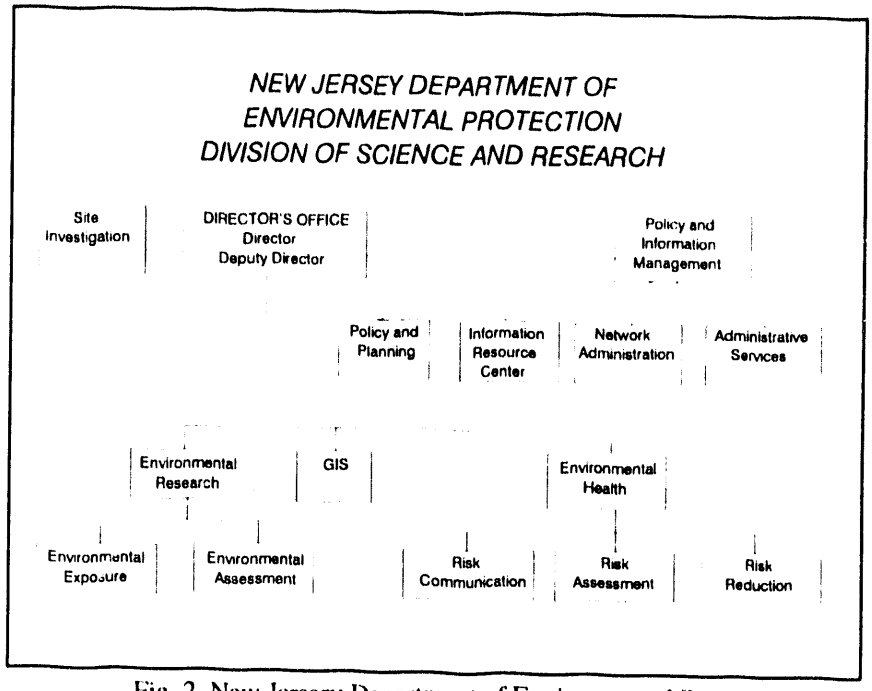

Fig. 2. New Jersery Department of Environmental Protection Division of Science and Research.

DSR has also provided partial funding, along with EPA and the California Department of Health Services, for the development of Risk Assistant, a software package that has databases on toxicity, chemical properties, exposure assumptions, ARARs, and analytical limits. When completed, Risk Assistant will be utilized by individuals with limited risk assessment training to assist with exposure and risk assessment of contaminated sites.

Research projects include bioavailability studies of dioxin and chromium from contaminated soils; determination of pesticide residues in crops grown or sold in New Jersey; and risk assessment based on these levels and others.

In addition to research projects, DSR is responsible for developing health based compound specific standards and guidance levels. A major project involved the development of health-based Maximum Contaminant Levels (MCLs) for 28 compounds, as required by the A-280 amendments to the New Jersey Safe Drinking Water Act, which require New Jersey to develop its own drinking water standards. New Jersey began this process

DSR participates in site-specific risk assessments on a case-by-case basis.

before EPA promulgated its first MCLs in 1987. The development of these drinking water standards by DSR involves evaluating the primary toxicology and epidemiology literature on the compound; developing a Support Document, which reviews background information and health effects; and performing the risk assessment for the compound. The documents were peer reviewed and became part of the basis and background for the regulations. As one of the leading states in the development of health-based drinking water standards, New Jersey actively participates in FSTRAC (Federal-State Toxicology and Regulatory Alliance), an organization of federal and state scientists that meets regularly to discuss issues relating to drinking water risk assessment.

DSR is also involved with the development of the human health basis for soil standards, groundwater guidance, and surface water quality standards.

Additionally, DSR participates in site-specific risk assessments on a case-by-case basis, particularly when the situation requires a nonstandard technical approach. For example, DSR is currently developing a risk assessment approach for chromium-contaminated sites in Hudson County, New Jersey. DSR has also participated in a contract funded by the Agency for Toxic Substances and Disease Registry through the New Jersey Department of Health to develop health assessments for Superfund sites in New Jersey. Finally, DSR provides technical consultation to NJDEP and to the public on questions relating to toxicology and risk assessment.

These varied activities require many types of information resources. Information is required from the basic scientific literature in a number of disciplines, from technical documents prepared by EPA and other federal and state agencies, and from regulatory sources such as the *Federal Register* and *New Jersey Register*.

NJDEP is fortunate to have its own library, the Information Resource Center (IRC), which was started with a TSCA (Toxic Substances Control Act) grant to states in the early 1980s. The IRC is part of DSR and serves the entire NJDEP. It has a staff of five, including three professional librarians. Its collection has a large emphasis on toxicology and environmental health and is also strong in the areas of water resources, waste management, hazardous substances, and chemical-specific information.

The chemical reference file includes information on approximately 2000 chemicals.

The collection includes approximately 2500 books, 5000 government documents, regulatory materials, and 125 journals. The chemical reference file, a collection developed by the IRC, includes information on approximately 2000 chemicals. The IRC also holds Toxic Release Inventory reports from New Jersey industries in 1987 and 1988.

The IRC uses interlibrary loan capabilities and can access federal technical documents.

The database searching capabilities of the IRC include both bibliographic and factual databases such as MEDLARS, Integrated Risk Information System (IRIS), and DIALOG. The use of these data bases allows for rapid access to the primary scientific literature on compounds of interest, as well as to summaries of their chemical and toxicological properties. The IRC uses

interlibrary loan capabilities, and can access federal technical documents. Although the library and its collections are open to the public, services for which fees are charged are available only to NJDEP staff.

All of these information resources are utilized extensively by the NJDEP technical staff and are invaluable in efficiently accessing the information needed to carry out the department's risk–assessment related work. These resources are indispensable in allowing NJDEP to perform risk assessment–related research and to develop original approaches toward health-based risk assessment.

Use of Information Resources by the State of Tennessee in Risk Assessment Applications

Bonnie S. Bashor, Tennessee Department of Health and Environment

The major resources used by the Bureau of Environment, and Environmental Epidemiology (EEP) for risk assessment are: the Integrated Risk Information System (IRIS), Health and Environmental Effects Summary Table (HEAST), Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles, databases at the National Library of Medicine (NLM), World Health Organization (WHO) Environmental Criteria, and documents that the Environmental Protection Agency (EPA) has published on Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) risk assessment activities. The Risk Assessment Review has been helpful in providing information about availability of new documents or information. No systematic method has been made available to us to locate information resources. IRIS User's Support has been helpful in making appropriate and timely referrals. Most other EPA resources were located by serendipity and persistence. The CERCLA methodology for risk assessments is being used in all environmental programs, and at present, one person is responsible for all risk assessment activities in the department, but plans are underway to train one or two people from each program area.

The Tennessee Department of Health and Environment (TDHE) is made up of four bureaus: Environment, Health Services, Medicaid, and Manpower and Facilities. All the environmental regulatory programs are within the Bureau of Environment, while risk assessment activities, health screening of environmental field workers, and health studies centered around pollution are within the Bureau of Health Services, Division of Environmental Epidemiology (EEP). See Figs. 1 and 2 for a description of the organization of TDHE. EEP is the link between the environmental programs and public health, dealing with health aspects of environmental pollution.

EEP began in 1982 as a very small program with no clear-cut goals or objectives. The division began slowly, but has built into a creditable program as its personnel learned about Environmental Epidemiology and acquired information on the toxicity of chemicals.

EEP began conducting risk assessments in 1983 when information was disclosed about mercury releases by the Department of Energy in Oak Ridge into East Fork Poplar Creek. Because estimates of a "safe" level of mercury in soil were not available at the time, EEP developed an equation for calculating such estimates.

Because estimates of a "safe" level of mercury in soil were not available at the time, EEP developed an equation for calculating such estimates.

Access to the Integrated Risk Information System (IRIS) has been especially helpful to EEP by providing timely, accurate toxicity information. Even with this resource, however, and with information available on TOXNET and MEDLINE and at national workshops, it was not until EPA began publishing its toxicity guidelines that EEP had sufficiently reliable data to confidently perform risk assessments.

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When the Division of Superfund (DSF) in 1988 asked EEP for assistance in learning to do risk

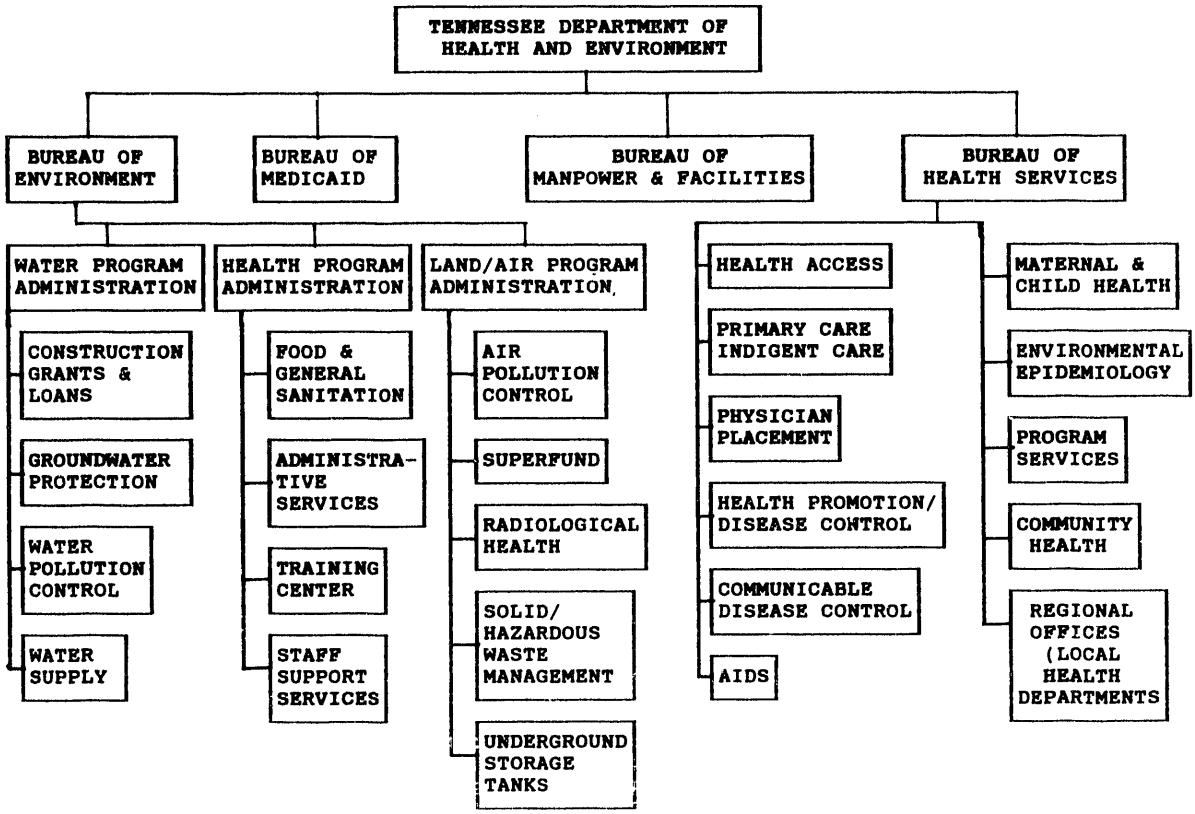

Fig. 1. Organizational chart for the Tennessee Department of Health and Environment.

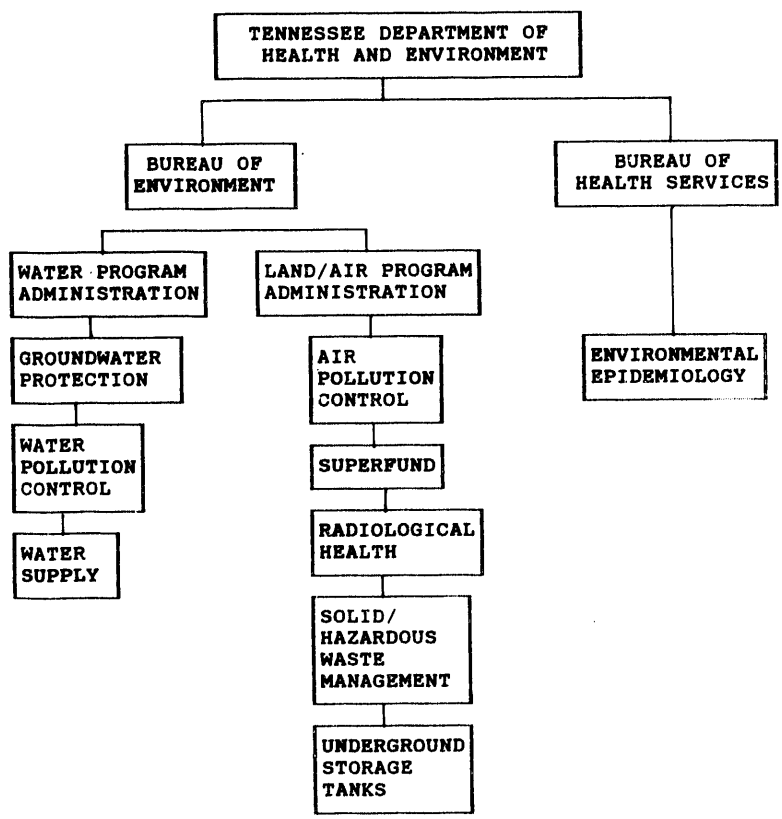

Fig. 2. Organization chart for Environmental Regulatory Programs and Environmental Epidemiology.

assessments, access to existing information proved to be difficult. Some of the most helpful resources that were ultimately obtained were EPA's guidelines published in: *The Superfund Exposure Assessment Manual, The Development of Statistical Distributions or Ranges of Standard Factors Used in Exposure Assessments, The Risk Assessment Guidance for Superfund, Volume 1, Human Health Evaluation Manual (Part A).* EEP uses these regularly, along with the periodical, *Risk Assessment Review,* which reports new information.

Although the publications department at EPA-Cincinnati is particularly helpful in sending hard copies of publications, when only a partial reference is available (as often happens in draft documents), it is difficult to find the person at EPA with information about the reference. The *Catalog of Superfund Program Publications* and the *EPA Information Resources Directory* are somewhat helpful in tracking down this kind of information. The division has been unable to acquire an EPA telephone directory but IRIS User Support has often directed EEP staff to the appropriate resource person. If there is a more timely way to get information on chemical toxicity, exposure assessments, or locating EPA publications than this personal contact network, the division would find it helpful. If resources are available that EEP has not found, information about them would be appreciated. EEP presently receives several journals and other publications. As funding increases, the division would like to subscribe to additional publications.

EEP is preparing a basic course in risk assessment for the DSF and for the Division of Solid Waste Management (SWM). Its purpose is to acquaint their engineers with the basics of toxicology, the definitions of slope factors and reference doses, and describe how these fit in the hazard identification and dose-response portions of risk assessments. The course will also cover exposure assessments and risk characterizations. EEP staff has worked in the field with environmental professionals to learn more about problems they face and to assist them in determining the sampling locations that are likely to provide the most useful information for determining risks to people living near Superfund sites.

EEP staff performs simple risk assessments for DSF to help their staff determine the urgency of actions to be taken to protect the public exposed to contaminants at Superfund sites.

EEP staff performs simple risk assessments for DSF to help their staff determine the urgency of actions to be taken to protect the public exposed to contaminants at Superfund sites. EEP also reviews risk assessments performed by contractors as part of the Remedial Investigation/ Feasibility Study (RI/FS) process.

Risk assessment in Tennessee is no longer limited to DSF. All environmental programs need risk assessment information in managing programs. EEP uses the process in assisting SWM to write and negotiate Resource Conservation and Recovery Act permits for which industries have requested Alternate Concentration Limits and to review the risk assessment portions of RI/FS documents. EEP used the risk assessment process to derive a water quality standard for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Risk assessment in Tennessee is no longer limited to DSF. All environmental programs need risk assessment information in managing programs.

(TCDD) for the Division of Water Pollution Control.

At the state level, hazard identification is limited to sampling to determine if toxic chemicals exist at a certain location. EEP seldom determines slope factors, reference doses, or No Observed Adverse Effect Levels (NOAEL). Therefore, EEP does not usually use laboratory data or academic publications to perform dose-response assessments. It is necessary, however, to understand the basis for dose-response calculations and the mechanisms of toxicity on which the calculations are based. On occasion, EEP has needed to use basic scientific information, as when a water quality standard was being derived for TCDD.

Environmental programs are using risk assessment processes more frequently. There is concern that resources have been and will continue to be missed because there is no systematic method to find them. No cooperative agreement exists with the ATSDR, which means that resource is of limited usefulness. There is also concern that EEP may lack adequate perspective and a system of checks and balances in its risk assessment process because there is no systematic way for EEP staff to discuss problems with other professionals.

EEP is doing a creditable job in performing risk assessments and health screening of TDHE's high-risk employees and in investigating potential disease clusters. The division would be most aided by continued expansion of IRIS, assistance in predicting concentrations of chemicals migrating from one medium to another, easy-to-use methods to calculate the number of needed samples, and current information about values for variables to use in exposure equations. Information on the use of biomarkers in exposed populations and methods of disease cluster analysis are also needed, as is information on the use of user-friendly geographical information systems.

There is concern that resources have been and will continue to be missed because there is no systematic method to find them. No cooperative agreement exists with the Agency for Toxic Substances and Disease Registry, which means that resource is of limited usefulness.

Integrated Risk Information System (IRIS)

Linda Tuxen, U.S. Environmental Protection Agency

The Integrated Risk Information System (IRIS) is an electronic information system developed by the U.S. Environmental Protection Agency (EPA) containing information related to health risk assessment. IRIS is the Agency's primary vehicle for communication of chronic health hazard information that represents Agency consensus following comprehensive review by intra-Agency work groups. The original purpose for developing IRIS was to provide guidance to EPA personnel in making risk management decisions. This role has expanded and evolved with wider access and use of the system. IRIS contains chemical-specific information in summary format for approximately 500 chemicals. IRIS is available to the general public on the National Library of Medicines's Toxicology Data Network (TOXNET) and on diskettes through the National Technical Information Service (NTIS). For further general information on IRIS and how to access the system contact: IRIS User Support (Staffed by Computer Sciences Corporation, USEPA, ECAO (MS-190), Cincinnati, Ohio, 45268. Telephone: (513) 569-7254, Facsimile: (513) 569-7916.

Background

Many U.S. Environmental Protection Agency (EPA) program offices and program support offices, including the Office of Research and Development, both at Headquarters and in EPA's ten Regional offices, are involved in assessment activities in support of various legislative mandates. In the 1980s, as health risk assessment became a more widespread practice across Agency programs, the need for greater consensus and consistency in the areas of hazard identification and dose-response assessment became clear. It was determined that an internal process should be established for reaching an Agency-wide judgment on the potential health effects of substances of common interest to these offices, and a system developed for communicating that Agency judgment to EPA risk assessors and risk managers. These would provide the needed consistency and coordination. In 1986, two EPA work groups with representation from program offices involved in risk assessment were convened to carry out such an internal process to reach consensus Agency positions on a chemical-by-chemical basis. In 1986, the Integrated Risk Information System (IRIS) data base was created for EPA staff as the official repository of that consensus information.

In the 1980's, as health risk assessment became a more widespread practice across Agency programs, the need for greater consensus and consistency in the areas of hazard identification and dose-response assessment became clear.

On June 2, 1988, a *Federal Register* (53 FR 20162) notice of public availability of IRIS was published. That notice described IRIS, the types of risk information it contains, and how to get access to the system. It informed the public about the establishment of the IRIS Information Submission Desk and the presence of a separate file on IRIS listing the substances scheduled for work group review. The submission desk was intended to provide opportunity for public input. The notice explained the procedures for submission of data or comments by interested parties on substances either on IRIS or scheduled for review by the work groups.

IRIS contains summaries of EPA qualitative and quantitative human health information that support two of the four major steps of the risk assessment process.

IRIS contains summaries of EPA qualitative and quantitative human health information that support two of the four major steps of the risk assessment process as outlined by the National Research Council (NRC 1983). That process consists of four major steps: hazard identification, dose-response evaluation, exposure assessment, and risk characterization. IRIS includes information in support of the first two of those steps, hazard identification and dose-response evaluation. Hazard identification is the qualitative determination of how likely it is that a substance will increase the incidence and/or severity of an adverse health effect. Dose-response evaluation is the quantitative relationship between the magnitude of the effect and the dose inducing such an effect. In general, quantitative human health hazard information, such as that in IRIS, is developed in light of numerous uncertainties involved in risk assessment, including those associated with extrapolations from animal data to humans and from high experimental doses to lower experimental doses to lower environmental exposures.

Exposure assessment is the evaluation of the nature and extent of exposure and the number and types of people exposed. IRIS does not include exposure assessment information. Combined with specific situational exposure assessment information, the summary health hazard information in IRIS may be used as one source in evaluating potential public health risks of, or from, environmental contaminants.

Risk characterization is the combining of the hazard identification assessment, dose-response evaluation, and exposure assessment to produce a synopsis and synthesis of all the data that should contribute to a conclusion with regard to the nature and extent of the risk. This includes discussion of the overall uncertainty in the analysis, including the major assumptions made, the scientific judgments employed, and an estimate of the degree of conservatism involved. IRIS contains limited information supporting the risk characterization step of the risk assessment process. That limited information in IRIS consists of brief statements on the quality of data and very general statements on confidence in the dose-response evaluation.

Quantitative human health hazard information, such as that in IRIS, is developed in light of numerous uncertainties involved in risk assessment.

Data Base Contents

The core of IRIS is the three consensus health hazard information summary sections: the reference dose (RfD) for non-cancer health effects resulting from oral exposure; the reference concentration (RfC) for non-cancer health effects resulting from inhalation exposure; and the carcinogen assessment for both oral and inhalation exposure. All of these terms are commonly used for judging the effects of lifetime exposure to a given substance or mixture.

In addition, an IRIS substance file may include supplemental information such as summaries of health advisories, regulatory actions, and physical/chemical properties.

The three consensus health hazard information summary sections are: the reference dose (RfD) for non-cancer health effects resulting from oral exposure; the reference concentration (RfC) for non-cancer health effects resulting from inhalation exposure; and the carcinogen assessment for both oral and inhalation exposure.

Non-Cancer Health Effects Information

An RfD is an estimate (with uncertainty spanning perhaps an

order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is believed likely to be without an appreciable risk of certain deleterious effects during a lifetime (EPA 1988). RfDs are developed by an assessment method that assumes that there is a dose threshold below which adverse effects will not occur. An RfD, which is expressed in milligrams per kilogram per day (mg/kg-day), is based on the determination of a critical effect from a review of all toxicity data and a judgment of the necessary uncertainty and modifying factors based on a review of available data. IRIS substance files contain the following information pertaining to the oral RfD: reference dose summary tables, principal and supporting studies, uncertainty and modifying factors used in calculating the RfD, a statement of confidence in the RfD, EPA documentation and review, EPA scientific contacts, and complete bibliographies for references cited.

RfDs are developed by an assessment method that assumes that there is a dose threshold below which adverse effects will not occur.

The inhalation reference concentration (RfC) is analogous to the oral RfD (EPA 1990) and is also based on the assumption that thresholds exist for non-cancer toxic effects. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extra-respiratory). The inhalation RfC is expressed in milligrams per cubic meter (mg/cu.m). The RfC method departs from that used to determine the oral RfD primarily by the integration of the anatomical and physiological dynamics of the respiratory system (i.e., portal-of-entry) with the physicochemical properties of the substance or substances entering the system. Different dosimetric adjustments are made according to whether the substance is a particle or gas and whether the observed toxicity is respiratory or extra-respiratory. These adjustments scale the concentration of the substance that causes an observed effect in laboratory animals (or in humans, when available from occupational epidemiology studies) to a human equivalent concentration for ambient exposures. IRIS substance files contain the following inhalation RfC information: reference concentration summary tables; description of dosimetric adjustment; principal and supporting studies; uncertainty and modifying factors used to calculate the RfC; a statement of confidence in the RfC; EPA documentation and review; EPA scientific contacts; and complete bibliographies for references cited.

Cancer Health Effects Information

The carcinogen assessment of an IRIS substance file contains health hazard identification and dose-response assessments developed from procedures outlined in the EPA Guidelines for Carcinogen Risk Assessment (51 FR 33992-43003, September 24, 1986). Each cancer assessment, as a rule, is based on an Agency document that has received external peer review. The hazard identification involves a judgment in the form of a weight-of-evidence classification of the likelihood that the substance is a human carcinogen. It includes the type of data used as the basis of the classification. This judgment is made independently of considerations

Each cancer assessment, as a rule, is based on an Agency document that has received external peer review.

of the strength of the possible response. The dose-response assessment is a quantitative estimate of the potential activity or magnitude of a substance's carcinogenic effect, usually expressed as a cancer unit risk. A cancer unit risk is an upper-bound on the increased likelihood that an individual will develop cancer when exposed to a substance over a lifetime at a concentration of either 1 microgram per liter (1 µg/L) in drinking water for oral exposure or 1 microgram per cubic meter (1 µg/cu.m) in air for continuous inhalation exposure. Generally, a slope factor for dietary use is also given. It is an upper-bound estimate of cancer risk for humans per milligram of agent per kilogram of body weight per day.

IRIS contains the following information in the cancer assessment section: EPA weight-of-evidence classification and its basis; a summary of human carcinogenicity studies when available; a summary of animal carcinogenicity studies; a summary of other data supporting the classification; oral and/or inhalation quantitative estimates; dose-response data used to derive these estimates and the method of calculation; statements of confidence in magnitude of unit risk; documentation and review; EPA scientific contacts; and complete bibliographies for references cited.

Scientific Contacts

It is important to note that in each of the three sections described above, EPA staff names and telephone numbers are included as scientific contacts for further information. The Agency believes that the inclusion of Agency scientific contacts able to discuss the basis for the Agency's position, has been very valuable. These individuals play a major role in providing public access to IRIS and a conduit for valued public comment.

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Bibliographies

IRIS contains full bibliographic citations for each substance file, directing the user to the primary cited studies and pertinent scientific literature. One of the major intents of IRIS was to encourage users to evaluate the primary literature used to develop the IRIS information in light of the assumptions and uncertainties underlying the risk assessment process.

Supplementary Information

In addition to the RfD, RfC, and carcinogenicity sections, IRIS substance files may contain one or more of three supplementary information sections: a summary of an Office of Water's Drinking Water Health Advisory, a summary of EPA regulatory actions, and a summary of physical/chemical properties. The only purpose of these supplemental sections is as accessory information to the consensus health hazard information. Since the primary intent of the IRIS date base is to communicate EPA consensus health hazard information, these other sections are only included as auxiliary material to provide a broader profile of a substance and are never added until at least one of the consensus health hazard sections described above (namely, the RfD section, RfC section, or carcinogenicity section) is prepared and approved for final inclusion

One of the major intents of IRIS was to encourage users to evaluate the primary literature used to develop the IRIS information in light of the assumptions and uncertainties underlying the risk assessment process.

on the data base. These supplemental sections should not be used as the sole or primary source of information on the current status of EPA substance-specific regulations.

Information Development Process

There are two EPA work groups, the Carcinogen Risk Assessment Verification Endeavor (CRAVE) and the Oral Reference Dose/ Inhalation Reference Concentration (RfD/RfC) Work Group, that develop the consensus health hazard information for IRIS. Each group consists of EPA scientists from a mix of pertinent disciplines and represents intra-Agency membership, and serves as the Agency's final review for EPA risk assessment information. When the work groups reach consensus on the health effects information and the dose-response assessment for a particular substance, the descriptive summary is added to IRIS.

Consensus generally means that no member office is aware of information that would conflict with the RfD, RfC, or cancer assessment, nor of analyses that would suggest a different value that is more credible. Such assurance rests on the capabilities of the individuals who represent their offices; thus, a large effort is conducted biannually to seek scientists who are both expert in this area of assessment and can represent their office.

The goals of the CRAVE are to reach Agency consensus on Agency carcinogen risk assessments; to arrive at a unified view on potential cancer risk from exposure to specific substances across Agency programs; and to identify, discuss, and resolve general issues associated with methods used to estimate carcinogenic risks for specific agents. The major outputs of the Work Group are summaries of risk information that have been previously developed and documented by scientific experts in Agency program and program support offices, and results of discussions of general issues in carcinogen risk assessment.

The purpose of the RfD/RfC Work Group is to reach consensus on oral RfDs and inhalation RfCs for non-cancer chronic human health effects developed by or in support of program offices and the Regions. The Work Group also works to resolve inconsistent RfDs or RfCs among program offices and to identify, discuss, and resolve generic issues associated with methods used to estimate RfDs and RfCs.

Conclusion

IRIS is not meant to be a comprehensive toxicological data base, a compendium of risk assessment knowledge, nor a sophisticated research tool. IRIS is primarily a communication system for the publication of EPA consensus human health hazard information. It directs users to the underlying animal and human data on which this risk information is based. Further, IRIS consensus health hazard information is not a completed risk assessment because, among other things, it contains no specific exposure assessment information and, thus, no complete risk characterization. A risk assessment, along with political, social, and economic considerations, may be

These supplemental sections should not be used as the sole or primary source of information on the current status of EPA substance-specific regulations.

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one of the bases of a risk management decision. Therefore, IRIS information is also not risk management information. Finally, because of the assumptions and uncertainties used in risk assessment, IRIS consensus information is provided with specific caveats and should be used carefully. It requires scientific judgment to properly use it as a tool for making risk-based decisions.

Reference

National Research Council. 1983. "Risk Assessment in the Federal Govemment: Managing the Process." Committee on the Institutional Means for Assessment of Risks to Public Health, Comission on Life Sciences, NRC. National Academy Press, Washington, D.C.

U.S. EPA. 1988. "Reference Dose [RfD]; Description and Use in Health Risk Assessment". *Regulatory Toxicology and Pharmacology* 8:471-86.

U.S. EPA. 1990. *Interim Methods for Development of Inhalation Concentrations.* EPA/600/8-90/066A.

Because of the assumptions and uncertainties used in risk assessment, IRIS consensus information is provided with specific caveats and should be used carefully.

Risk Assessment and Toxicology Databases for Health Effects Assessment

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Scientific and technological developments bring unprecedented stress to our living environment. Society is in the position of having to predict the results of potential health risks from technologically based actions that may have serious, far-reaching consequences. The potential for error in making such predictions or assessments is great and multiplies with the increasing size and complexity of the problem being studied. Because of this, the availability and use of reliable data is the key to any successful forecasting effort. Scientific research and development generate new data and information. Much of the scientific data being produced daily is stored in computers for subsequent analysis. This situation provides both an invaluable resource and an enormous challenge. With large amounts of government funds being devoted to health and environmental research programs and with maintenance of our living environment at stake we must make maximum use of the resulting data to forecast and avert catastrophic effects. Along with the development of large databases have come various levels of accuracy. The data used in predictive studies must be accurate and readily available. The most efficient means of obtaining the data necessary for assessing the health effects of chemicals is to utilize databases and other resources specifically designed and developed for this purpose. Resources available for risk assessment applications include the toxicology databases and information files developed at ORNL. To make the most efficient use of the data/information that has already been prepared, attention and resources should be directed toward projects that meticulously evaluate the available data/information and create specialized peer-reviewed value-added databases. Examples of such projects and databases include the U.S. Environmental Protection Agency's (EPA) Gene-Tox Program that produces the Gene-Tox Database, the National Library of Medicine's Hazardous Substances Data Bank, and the U.S. Air Force Installation Restoration Toxicology Guide. These and similar value-added toxicology databases were developed at ORNL and are being maintained and updated. These databases and supporting information files, as well as some data evaluation techniques are discussed in this paper with special focus on how they are used to assess potential health effects of environmental agents.

Introduction

The scientific community is one of the largest producers and consumers of information. Advances in science are fueled by the use of information, and for this reason its access and use should be facilitated. However, significant impediments exist. For instance, an intrinsic problem touching all areas of scientific endeavor is that information is accumulating at a rate that overwhelms individual or collective efforts to keep up with and take advantage of it. Because advances within a particular scientific discipline are greatly influenced by the availability and utilization of existing information, it stands to reason that everything possible should be done to ensure that no impediments exist to the ready access of that information.

The level of effort being exerted within some disciplines (such as toxicology) to effect unimpaired and easy access to information is significant; however, funding for this effort is not equal to that appropriated for research. This imbalance in funding creates a paradox because increased funding levels for research mean that greater amounts of information will be generated and published, thus overwhelming the access capabilities of users. Hence, the entities within government, industry, and the private sector that fund research should also be motivated to provide adequate financial support for the manage-

Information is accumulating at a rate that overwhelms individual or collective efforts to keep up with and take advantage of it.

ment, access, and use of the information derived from or generated by their research dollars. Information facilities shown to be of proven value should be viewed as permanent national resources for the advancement of science and the understanding of scientific discovery.

Because information availability is vital to the success and advancement of scientific endeavors such as assessing possible health hazards from environmental agents, it is imperative that those making decisions regarding the safety of environmental agents know how to maximize the available information resources. Access to relevant and reliable information is essential to the proper planning and conduct of any research project and is absolutely necessary for conducting health risk assessments. The foundation of all research studies and health risk assessments is the scientific literature. To obtain the experimental data needed to make a health risk assessment, one must either go to the primary toxicology literature or make use of a reliable specialized information resource.

This paper discusses the dilemma faced by individuals who must assess human health risks from environmental agents in their quest to find quality toxicology information and evaluated data for use in assessing health hazards. Federal and state laws require that such assessments be made (Table 1). The paper also describes how certain resources that have either been developed or are available from ORNL can be used to derive maximum benefit of available evaluated or peer-reviewed databases for specific

Table 1. Federal laws governing exposures to toxic substances (grouped by year law became effective)[a]

Legislation	Agency[b]	Area of concern
Food, Drug and Cosmetics Act (1906, 1938, amended 1958)	FDA	Foods, drugs, cosmetics, food additives, new drugs, animal and feed additives, medical supplies
Federal Insecticide, Fungicide and Rodenticide Act (1947, amended 1960, 1962, 1968, 1972, 1975, 1976, 1978, 1984, 1988)	EPA	Pesticides
Dangerous Cargo Act (1952)	DOT, USCG	Water shipment of toxic materials
Atomic Energy Act (1946, amended 1954, 1959, 1964, 1983, 1986,1988)	NRC, DOE, EPA	Radioactive substances
Federal Hazardous Substances Act (1960, amended 1988)	CPSC	Toxic household products
Federal Meat Inspection Act	USDA	Food, feed, color additives and pesticide residues
Occupational Safety and Health Act (1970)	OSHA, NIOSH	Workplace toxic chemicals
Poison Prevention Packaging Act (1970, amended 1983, 1984)	CPSC	Packaging of hazardous household products
Clean Air Act, 1955 [amended 1963, 1966, 1967 (called Air Quality Act), 1970, 1977, 1983, 1990]	EPA	Air pollutants
Hazardous Materials Transportation Act (1974, amended 1990)	DOT	Transport of hazardous materials
Water Quality (1987) (formerly Clean Water Act 1948), and Federal Water Pollution Control Act (1972, amended 1977, 1978)	EPA	Water pollutants
Marine Protection, Research and Sanctuaries Act (1972, amended 1984, 1986, 1987)	EPA	Ocean dumping of hazardous substances
Consumer Product Safety Act (1972, amended 1981)	CPSC	Hazardous consumer products
Lead-Based Paint Poison Prevention Act (1973, amended 1976)	CPSC, HHS, HUD	Use of lead paint in federally assisted housing
Safe Drinking Water Act (1974, amended 1976, 1977, 1979, 1980, 1984, 1986)	EPA	Drinking water contaminants
Resource Conservation and Recovery Act (1976, amended 1984, 1986)	EPA	Solid waste, including hazardous waste
Toxic Substances Control Act (1976, amended 1986, 1988)	EPA	Hazardous chemicals not covered by other laws, includes premarket review
Uranium Mill Tailings Radiation Control Act (1978, amended 1988)	EPA	Uranium and thorium tailings
Federal Mine Safety and Health Act (1977)	DOL, NIOSH	Toxic substances in coal and other mines
Nuclear Waste Policy Act (1982, amended 1988)	NRC, EPA	Radioactive wastes
Radon Gas and Indoor Air Quality Act (1986)	EPA	Radon gases, air pollutants

continued

Table 2. Sampling of secondary on-line bibliographic and/or numeric information sources containing toxicological information

Name	File, number of records, and period covered	File description
BRS Bibliographic Retrieval Services, Latham, N.Y.	BIOSIS Previews 7,196,209 1969-present	BIOSCIENCES INFORMATION SERVICE Worldwide coverage of research in the life sciences from more than 9000 journals, as well as monographs, reports, and symposia proceedings. Subjects include microbiology, plant and animal science, biochemistry, botany, environmental biology, experimental medicine, genetics, public health, toxicology, virology, and other interdisciplinary areas. Citations from both *Biological Abstracts* and *Biological Abstracts*/RRM
	CA SEARCH 8,900,000 1967-present	CHEMICAL ABSTRACTS SERVICE (CAS) Bibliographic data, keyword phrases, index entries, general subject headings, and CAS Registry Number(s) for documents covered by *Chemical Abstracts Service*
	HAZARDLINE 4,000 substances	OCCUPATIONAL HEALTH SERVICES, INC. Provides chemical names, formula, CAS Registry Number(s), Registry of Toxic Effects of Chemical Substances (RTECS) number, physical description, chemical and physical properties, toxicology, permissible exposure levels, symptoms of exposure, disposal methods, protective procedures, test references, government regulations, and many other areas of information on specific chemical substances
	MEDLINE MEDLARS On-Line 7,000,000 1966-present	NATIONAL LIBRARY OF MEDICINE Contains references from more than 3000 biomedical journals published throughout the world. Monographs and conference proceedings added in 1976. Corresponds to *Index Medicus*. Contains full bibliographic citations and index terms for all records. Some abstracts included. *SDILINE*, the monthly update to the main file, used for current awareness service
CAS ONLINE Chemical Abstracts Service American Chemical Society Columbus, Ohio	CAS ONLINE Chemical Search System from Chemical Abstracts Service 8,900,000 1967-present	Equivalent of the printed *Chemical Abstracts* (CA). Bibliographic data, keyword phrases, index entries, general subject headings, and CAS Registry Number(s) for chemistry-related publications in 50 languages from 150 countries. Includes worldwide patent documents. Easy crossover to the *CAS CHEMICAL REGISTRY*
	CAS CHEMICAL REGISTER 10,000,000 compounds	The world's largest file of substance information, including coordination compounds, polymers, incompletely defined substances, alloys, mixtures, and minerals. In each record the registry number is linked to molecular structure diagram, molecular formula, CA index name, synonyms, and the ten most recent references in *Chemical Abstracts*. Easy crossover to the bibliographic file
DIALOG Dialog Information Services, Inc. Palo Alto, Calif.	EMBASE 4,311,401 June 1974-present	EXCERPTA MEDICA Abstracts and citations of articles from over 4000 biomedical journals published throughout the world. Covers entire field of human medicine and related disciplines
		ENERGYLINE Comprehensive coverage of 20 different energy-related areas, including environmental impact
		ENVIROLINE Covers the world's environmental information by indexing and abstracting more than 5000 international primary and secondary source publications reporting on all aspects of the environment. Also includes rulings from the *Federal Register* and patents from the *Official Gazetta*
	INTERNATIONAL PHARMACEUTICAL ABSTRACTS 175,587 1970-present	AMERICAN SOCIETY OF HOSPITAL PHARMACISTS More than 650 pharmaceutical, medical, and related journals are indexed and abstracted

areas of toxicology. To properly focus on these issues, it is necessary to look at the evolutionary history of toxicology information files during the last 20 years. Such a review provides an understanding of the usefulness of specific information files as well as the quality assurance measures used in their creation. The historical development of toxicology information resources has recently been adroitly addressed elsewhere (Kissman and Wexler 1983; Wassom and Lu 1992).

Table 1. Federal laws governing exposures to toxic substances (grouped by year law became effective)[a]

Legislation	Agency[b]	Area of concern
Comprehensive Environmental Response, Compensation, and Liability Act (Superfund) (1980, amended 1986)	EPA	Hazardous substances, pollutants and contaminants
Asbestos Hazard Emergency Response Act (1986)	EPA	Asbestos
Emergency Planning and Community Right-to-Know Act (1986)	EPA	Hazardous substances, toxic chemicals, pollutants, and contaminants
Medical Waste Tracking Act (1988)	EPA	Medical wastes
Oil Pollution Act (1990)	EPA	Oil pollutants in water

[a]Adapted from *Fed. Regis.* 50 (50), 10373-10374, March 14, 1985, and *Environmental Laws*, Bureau of National Affairs, 1985.

[b]CPSC, Consumer Product Safety Commission; DOL, Department of Labor; DOT, Department of Transportation; EPA, Environmental Protection Agency; FDA, Food and Drug Administration; HHS, Department of Health and Human Services; HUD, Department of Housing and Urban Development; NRC, Nuclear Regulatory Commission; NIOSH, National Institute of Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; USCG, United States Coast Guard; and USDA, United States Department of Agriculture; DOE, Department of Energy.

State of the Toxicology Literature and Problems of Access

The literature of toxicology and the information contained in it are increasing at an exponential rate (Lu and Wassom 1985). A number of bibliographic and/or numeric on-line databases are available to assist investigators engaged in scientific research and risk assessment to access the toxicology literature (Table 2). To obtain maximum use of these databases, users should consider the strengths and weaknesses of each. These factors must be recognized to ensure the most appropriate application of the database to find information for a particular need. For example, the emphasis placed on quality control among these databases varies. Rigid quality assurance guidelines are not part of the operational procedures of most databases, handicapping their effective use.

Evolution of Toxicology Databases

During the 1960s, toxicology became recognized as a science in its own right. Along with this recognition came the formation of two separate Presidential Science Advisory Committees (PSAC) that issued in-depth reviews and commentary regarding the current and future needs with respect to the collection, storage, retrieval, and use of scientific and technical information. These reports had a profound effect on the future of toxicology information that, up until the 1960s, was primarily library-based and scattered among several large-scale multidisciplinary indexing and abstracting services. These include Chemical Abstracts, Biological Abstracts, Index Medicus, and Excerpta Medica. A PSAC report published in 1963 entitled "Science, Government, and Information" stated, "The technical community must recognize that handling technical information is a worthy and integral part of science"

These reports had a profound effect on the future of toxicology information.

Table 2. Sampling of secondary on-line bibliographic and/or numeric information sources containing toxicological information

Name	File, number of records, and period covered	File description
	LIFE SCIENCES COLLECTION 1,254,581 1978-present	CAMBRIDGE SCIENTIFIC ABSTRACTS Abstracts of worldwide literature in the fields of animal behavior, biochemistry, ecology, entomology, genetics, immunology, microbiology, toxicology, and virology
	MEDLINE	See entry under BRS system
	NTIS	The National Technical Information Service (NTIS) is the central source for the public sale and dissemination of U.S. government-sponsored research. The database consists of unclassified government-sponsored research, development, and engineering reports, as well as other analyses prepared by government agencies, their contractors, or grantees. The database corresponds to *Government Reports Announcements & Index.*
	OCCUPATIONAL SAFETY AND HEALTH (NIOSH) 162,316 1973-present	U.S. NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH TECHNICAL INFORMATION CENTER Includes citations to more than 400 journal titles as well as over 70,000 monographs and technical reports
	POLLUTION ABSTRACTS	Pollution abstracts is a leading resource for references to environmentally related technical literature on pollution, its sources and its control. Produced by Cambridge Scientific Abstracts, the database corresponds to the printed *Pollution Abstracts.*
	SCISEARCH 10,029,029 1974-present	INSTITUTE FOR SCIENTIFIC INFORMATION Multidisciplinary index to the literature of science and technology, including animal and plant science, biochemistry, drug research, experimental medicine, and microbiology. Unique feature is indexing cited papers. Corresponds to the printed *Science Citations Index*
MEDLARS National Library of Medicine Bethesda, Md.	CANCERLIT Cancer Literature 806,157 1963-present	NATIONAL CANCER INSTITUTE Cancer therapy and chemical, physical, and viral carcinogenesis from *Carcinogenesis Abstracts* and *Cancer Therapy Abstracts*
	MEDLINE	See entry under BRS system
	RTECS 100,000 chemicals	NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH AND SAFETY Provides chemical names, formula, CAS Registry Number(s), RTECS number, physical description, chemical and physical properties, toxicology, permissible exposure levels, symptoms of exposure, disposal methods, protective procedures, test references, government regulations, and many other areas of information on specific chemical substances
	TOXNET Toxicology Data Network	A computerized system consisting of a collection of selected toxicology-oriented databases and information files. Environmental Mutagen Information Center (EMIC) File Environmental Teratology Information Center (ETIC) File Development and Reproductive Toxicology (DART) File Hazardous Substances Data Bank (HSDB) Chemical Carcinogenesis Research Information System (CCRIS) U.S. Environmental Protection Agency Genetic Toxicology Database (Gene-Tox) Registry of Toxic Effects of Chemical Substances (RTECS) Directory of Biotechnology Information Resources (DBIR) Toxic Chemical Release Inventory (TRI) U.S. Environmental Protection Agency Integrated Risk Information System (IRIS)

Table 2. Sampling of secondary on-line bibliographic and/or numeric information sources containing toxicological information

Name	File, number of records, and period covered	File description
	TOXLINE Toxicology Information On-Line Current File: 1981-present > 100,000 Backfiles (TOXBACK): 1980 and older material > 1,160,000	An extensive collection of toxicology information with references to human and animal toxicity studies, effects of environmental chemicals, pesticides, and pollutants, adverse drug reactions, and analytical methodology. Abstracts and/or indexing terms included in addition to full bibliographic citations. Information derived from secondary sources and special collections of material: Environmental Mutagen Information Center (EMIC) File Environmental Teratology Information Center (ETIC) File Epidemiology Information System (EPIDEM) Federal Research in Progress (FEDRIP) International Labour Office (CIS) International Pharmaceutical Abstracts (IPA) NIOSHTIC (NIOSH) Pesticides Abstracts (PESTAB) Poisonous Plants Bibliography (PPBIB) Toxicity Bibliography (from MEDLINE) (TOXBIB) Toxicology Document and Data Depository (NTIS) Toxicological Aspects of Environmental Health (BIOSIS) Toxicology Research Projects (CRISP) Toxic Substances Control Act Test Submissions (TSCATS)
	TOXLIT and TOXLIT 65	A collection of bibliographic citations and abstracts assembled by the Chemical Abstracts Service under the title of *Chemical-Biological Activities* (CBC). The specific focus of this collection is the pharmacological, biochemical, physiological, and toxicological effects of drugs and other chemicals
ORBIT System Development Corporation Santa Monica, Calif.	PESTDOC approximately 300,000 1968-present	DERWENT PUBLICATIONS LIMITED Covers worldwide journal literature on pesticides, herbicides, and plant protection. Includes analysis, biology, chemistry, and toxicology
	RINGDOC Pharmaceutical Literature Documentation approximately 1.2 million 1976-present	DERWENT PUBLICATIONS LIMITED Covers scientific journal literature on pharmaceuticals. Specifically designed to meet the information requirements of manufacturers. Includes papers from over 750 worldwide journals
	VETDOC Veterinary Literature Documentation approximately 96,000 1968-present	DERWENT PUBLICATIONS LIMITED Covers journal literature concerning developments and usage of drugs, hormones, vaccines, growth promoters, etc., in farm and domestic animals. Includes analysis, chemistry, therapeutics, pharmacology, toxicology, and management

(President's Science Advisory Committee 1963). In 1966, the PSAC published another report on the "Handling of Toxicological Information" (President's Science Advisory Committee 1966). This report defined toxicology information as "All information descriptive of the effects of chemicals on living organisms or their component subsystems" and further indicated the necessity of a ". . . computer-based comprehensive exhaustive system for storage and retrieval of valid information on the interaction between chemicals and biological systems."

These two reports set the direction and development of toxicological databases during the two decades since their publication. Correlated with the increased need for and use of computerized toxicology databases has come the appearance and proliferation of computer software and hardware to facilitate manipulation of information in these databases. The notable developments in this area have been supported by unprecedented quantum leaps in electronic technology. Further details regarding the evolving nature of toxicology databases and information files are provided in another paper in these symposium proceedings (Wassom and Lu 1992).

Types of Toxicology Databases and Information Resources

As shown in Table 2, an array of toxicological and chemical information resources are available for the researcher. These resources have been catalogued in other publications, and the reader should consult these publications for a more complete listing (Kissman 1980; Wassom 1980; Akland and Waters 1983; Lu and Wassom 1985). The majority of the current toxicological information files are literature-based or oriented toward specific subject matter such that a single record equals a published paper.

Other types of toxicological databases are available that are constructed around a specific subject, such as a chemical. In such a file, a single record equals one specific chemical. Such chemical-oriented files can be classified as (1) numerical/factual—records contain data that has been peer reviewed or (2) numerical/factual—records contain data that has not been peer reviewed. Examples of these two classifications are the Hazardous Substances Data Bank (HSDB) and the Registry of Toxic Effects of Chemical Substances (RTECS) [TOXNET 1991], respectively. These files are discussed more fully in a later section.

The variety of toxicology information files and the increasing number of computerized retrieval systems presents users with two major problems: (1) the rapidly growing volume of accessible literature and (2) the incompatibility of the various computer files. To these two problems we add a third, quality assurance that will always be the most critical and controversial of all.

How can these problems be overcome to maximize available resources? For toxicology, this can only be achieved by using those resources that have proven utility and merit. In the following sections we suggest ways to maximize the toxicology infor-

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mation resources now available. Currently, only a small number of peer-reviewed or value-added databases exist that are useful to individuals interested in the areas of genetic toxicology, carcinogenicity, developmental toxicology, or teratogenicity. These sources are shown in Table 3 and are described in the following section.

Table 3. Short-term bioassays reviewed by the Gene-Tox Program

Assays Detecting Gene Mutation

Salmonella typhimurium (histidine reversion test) — use of one or more of the five standard strains (TA98, TA100, TA1535, TA1537 and TA1538)
Escherichia coli WP2 — reverse mutation studies
Escherichia coli WP2*uvr*A — reverse mutation studies
Host-mediated assay studies
Body fluid assay — urine
Saccharomyces cerevisiae — forward mutation studies
Saccharomyces cerevisiae — reverse mutation studies
Schizosaccharomyces pombe — forward mutation studies
Schizosaccharomyces pombe — reverse mutation studies
Aspergillus — forward mutation studies
Aspergillus — reverse mutation studies
Neurospora crassa — forward mutation studies
Neurospora crassa — reverse mutation studies
Chinese hamster ovary cells in culture — gene mutation at HGPRT locus
Mouse lymphoma (L5178Y) cells in culture — gene mutation at TK locus
Chinese hamster lung cells in culture — gene mutation studies, all loci
Drosophila melanogaster— sex-linked recessive lethal test
Mouse spot test
Mouse specific locus test — all tests
Plant gene mutation studies — grouping of tests with Arabadopsis, Glycine, Hordeum, Tradescantia, and *Zea mays*

Assays Detecting Chromosomal Effects

Saccharomyces cervisiae — aneuploidy studies
Aspergillus—aneuploidy studies
Neurospora crassa — aneuploidy studies
Plant chromosome studies — grouping of tests with Allium, Hordeum, Tradescantia, and Vicia
Drosophila melanogaster aneuploidy studies — whole sex chromosome loss
Drosophila melanogaster aneuploidy studies — sex chromosome gain
Drosophila melanogaster aneuploidy studies — sex chromosome loss
Drosophila melanogaster heritable (reciprocal) translocation test
Mammalian cytogenetics — all in vitro cell culture studies, nonhuman studies
Mammalian cytogenetics — all in vivo bone marrow studies, nonhuman studies
Mammalian cytogenetics — all in vivo lymphocyte or leukocyte studies, nonhuman
Mammalian cytogenetics — all male germ cell studies
Mammalian cytogenetics — in vivo oocyte or early embryo studies
Micronucleus test — mammalian polychromatic erythrocyte assay, all species
Micronucleus test — plant
Micronucleus test — in vitro mammalian cell culture studies, nonhuman
Micronucleus test — in vitro human lymphocyte studies
Dominant lethal test — rodents
Heritable translocation test — rodents
Mammalian cytogenetics — in vitro cell culture studies, human
Mammalian cytogenetics — in vitro lymphocyte or leukocyte studies, human
Mammalian cytogenetics — in vivo bone marrow studies, human
Mammalian cytogenetics — in vivo lymphocyte or leukocyte studies, human

Assays Detecting Other Types of Genotoxic Effects

*Escherichia coli pol*A (W3110-P3478) — all tests without S9
*Escherichia coli pol*A (W3110-P3478) — all tests with S9
Bacillus subtilis rec (H17-M45) — spot test
Bacillus subtilis rec (H17A-45T) - spot test
Saccharomyces cerevisiae — gene conversion studies
Saccharomyces cerevisiae — homozygosis studies through recombination
Aspergillus — crossing-over studies
Unscheduled DNA synthesis in mammals — studies with rat primary hepatocytes
Unscheduled DNA synthesis in mammals — studies with mouse germ cells
Sister chromatid exchange — in vitro studies, nonhuman
Sister chromatid exchange — in vivo studies, nonhuman
Effects on mammalian sperm — rat studies
Effects on mammalian sperm — mouse sperm morphology studies
Effects on mammalian sperm — rabbit studies
Effects on mammalian sperm — mouse, F_1 assay studies
Unscheduled DNA synthesis in mammals — in vitro studies, human diploid fibroblast
Sister chromatid exchange — in vitro studies, human cells
Sister chromatid exchange — in vitro studies, human embryonic lung fibroblasts (WI-38 cells)
Sister chromatid exchange — in vitro studies, human lymphocytes
Sister chromatid exchange — in vivo studies, human lymphocytes
Effects on mammalian sperm — human studies

Table 3 *(Continued)*

Assays Detecting Cell Transformation and Carcinogenicity

Cell transformation studies — BALB/c-3T3 cells
Cell transformation studies — C3H/10T1/2 cells
Cell transformation studies — mouse prostate cells
Syrian hamster embryo — clonal assay
Syrian hamster embryo — focus assay
Cell transformation studies — RLV/1706 cells (Fischer rat embryo cells)
Cell transformation studies — AKR/ME cells (mouse embryo cells)
Cell transformation studies — SA7/SHE cells (Syrian hamster embryo cells)
Cell transformation Studies — SA7/RAT cells (Fischer)
Mammalian carcinogenicity — animal in vivo studies, nonhuman

Value-Added or Peer-Reviewed Toxicology Databases

U.S. EPA Gene-Tox Database

Perhaps the best illustration or perspective on the issue of quality within the realm of the current toxicology literature comes from the EPA's Genetic Toxicology (Gene-Tox) Program (Waters and Auletta 1981). The Gene-Tox Program is a systematic evaluation of selected short-term bioassays for detecting mutagenicity and presumptive carcinogenicity. Sponsored and directed by the Office of Testing and Evaluation within the EPA Office of Pesticides and Toxic Substances, the EPA uses Gene-Tox as a resource in establishing standard genetic testing and evaluation procedures for the regulation of toxic substances. Gene-Tox also helps to determine the direction of research and development in the field of genetic toxicology (Russell et al. 1984, Brusick and Auletta, 1985, Dearfield et al. 1991).

The Gene-Tox database, a product of the Gene-Tox Program, is now available on-line through the National Library of Medicine's TOXNET system (Vasta and Wexler 1985). Information from Gene-Tox is also included in chemical records of HSDB, and locator tags are also placed on chemical records in the RTECS file.

In the initial phase (Phase I) of the Gene-Tox Program, 23 panels (each consisting of 5 to 10 scientists) reviewed the existing literature from ORNL's Environmental Mutagen Information Center (EMIC) information file through mid-1979 and prepared reports on the applicability and performance of each selected bioassay (Table 3). The data were edited and placed in a computer file. During subsequent phases of Gene-Tox (Phases II and III) the literature through 1990 was reviewed for selected assays. To date, information on over 4600 different chemicals has been entered into the database. The distribution of these compounds among the various short-term bioassays (64 genetic toxicology and 9 cell transformation) reviewed by Gene-Tox is sporadic. Some bioassays have results on less than ten compounds (e.g., the in vivo sister chromatid exchange test with human lymphocytes has only one), whereas other bioassays, such as the Ames/Salmonella test, have more than 2000. Evaluated in vivo carcinogenicity results on 392 compounds are also available in the Gene-Tox file.

The structural classification of all Gene-Tox evaluated compounds, as they occur within a

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given bioassay, show an erratic clustering pattern with respect to their common structural characteristics. This clustering or distribution, of course, varies with respect to the number of compounds tested in each bioassay.

During the Gene-Tox process, some provocative insights into the quality of the literature were revealed. It was shown that most journals failed to maintain a strict editorial policy with respect to format, data presentation, and the inclusion or referencing of key or essential information elements regarding such obviously vital items as specific details of agent(s) tested, control data, experimental design, and/or protocol used. Because of these deficiencies, only 52% of the papers reviewed were used in Gene-Tox; it is indeed interesting that almost half (48%) of the literature was, for one reason or another, not used. Some of the papers in this latter category were not used because they were either written in a foreign language, not published in a refereed source, or did not contain original data. The majority, however, did not meet the rigid criteria established by the various Gene-Tox review panels. The criteria used for each specific bioassay reviewed by Gene-Tox may be found in the various published panel reports for each bioassay. The number of papers used varied with each panel and bioassay. For example, the Chinese hamster ovary (CHO) cell gene mutation panel used only 8% of the papers screened (Hsie et al. 1981).

DeMarini and Shelby (1984) recently commented on the state-of-the-scientific literature and the lack of published data to properly evaluate test results. These authors, in a survey of the literature, found that papers often omitted certain key information necessary for readers to make an independent evaluation of the reported results and conclusions. An appeal was issued to authors, reviewers, and journal editors to recognize this problem and institute measures to correct it. Primarily because of the Gene-Tox Program's review of the 1960-1979 literature and subsequent recommendations on assay protocols and data reporting, the percentage of literature published during the 1980–1988 era and used by Gene-Tox to update results from the 1980–1988 literature for several selected assays increased noticeably. 75 to 90% of the literature was used compared to the dismal showing of 8 to 25% from the 1969–1979 literature.

During the current update (Phase III) of the Gene-Tox Program, panels of scientists are critically evaluating the reports published by the program for each bioassay and comparing the test results between specific assays or assay groups on a chemical-by-chemical and chemical class basis (Ray et al. 1987). For this evaluation, attempts will be made to determine the sensitivity of the tests to specific classes of chemicals and to identify major strengths and weaknesses of each bioassay. The database resulting from the Gene-Tox Program is the most comprehensive collection of evaluated genetic toxicology data available. Work is under way to keep this database updated at regular intervals with material screened from papers in the EMIC file selected from the

The criteria used for each specific bioassay reviewed by Gene-Tox may be found in the various published panel reports.

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current literature. Thus far, the Gene-Tox Program has evaluated over 4600 chemicals as tested in 1 or more than 23 genetic toxicology bioassays.

International Agency for Research on Cancer Monographs

In 1971, the International Agency for Research on Cancer (IARC) initiated a program to evaluate the carcinogenic risk of chemicals to humans (Tomatis 1988). The object of the program was to provide government authorities with expert independent scientific opinions regarding environmental carcinogenesis through the publication of critical reviews of carcinogenicity and related data. The aim of IARC is to evaluate possible human carcinogenic risk from detailed review and analysis of pertinent literature. IARC's work is partially funded by the National Cancer Institute.

The IARC Monographs summarize evidence for the carcinogenicity of individual chemicals and other relevant information on the basis of data compiled, reviewed, and evaluated by a working panel of experts. Priority is given to chemicals, groups of chemicals, or industrial processes for which there is at least some suggestion of carcinogenicity, either from evidence of human exposure and/or observations in animals. It should be emphasized that the inclusion of a particular compound in an IARC volume does not necessarily mean that it should be considered carcinogenic nor does the fact that a chemical is absent from an IARC review imply that it is not a carcinogenic hazard. As new data become available on chemicals for which Monographs have already been prepared and/or new principles for evaluation become available, reevaluations may be made at subsequent IARC meetings. If the new evidence warrants, revised Monographs will be published.

The IARC Monographs are distributed internationally to governmental agencies, industries, and scientists. They are also offered to any interested person through World Health Organization publication outlets.

Through August 1991, 52 volumes of the Monographs and several supplements had been published. These volumes contain indexes both for chemical name and molecular formula as well as Chemical Abstracts Service Registry Number(s). More than 960 chemicals or chemical groups were reviewed by IARC through monograph vol. 52. Carcinogenicity evaluations have not been made on all the chemicals reviewed because either no data were available or the data available to IARC were judged inadequate for evaluation. Specialized information files and databases developed at ORNL, such as EMIC, the Environmental Teratology Information Center (ETIC) file, and the Gene-Tox database, are used routinely by IARC in the production of their monographs.

In a survey of 751 users conducted in January 1991, some interesting facts regarding use of the monographs were obtained. The most important uses of the monographs are (1) a source of epidemiological studies (68%); (2) a general overview of carcinogenicity (63%), (3) detailed infor-

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mation on animal carcinogenicity studies (57%), (4) detailed information on other toxic effects (48%), (5) an overview of data on other toxic effects (34%), (6) background information for regulatory action (32%), and (7) application of evaluation in regulatory action (18%). Overall, 71% of the individuals surveyed found the monograph a useful source of information (Vainio, H., personal communication to John S. Wassom, September 5, 1991).

Hazardous Substances Data Bank

The Hazardous Substances Data Bank (HSDB), formerly called the Toxicology Data Bank, was originated by the National Library of Medicine (NLM) in the early 1970s. HSDB is a numerical/factual database composed of over 4300 comprehensive chemical records (Oxyman et al. 1970, Vasta and Wexler 1985, TOXNET 1991). These records contain approximately 140 different data elements, which are grouped into ten categories and administrative information. These categories include pharmacological and toxicological data (e.g., LD_{50} values), environmental and occupational information, manufacturing and use data, regulatory information, and analytical methods, as well as information on the chemical and physical properties of each chemical. Components included in the toxicology category are shown in Table 4. Substances selected for HSDB include high-volume production or exposure chemicals, drugs and pesticides exhibiting potential toxicity or adverse effects, and other substances subject to regulation under the provisions of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (Superfund) and the Superfund Amendment Reauthorization Act (SARA) of 1986.

Table 4. Data elements of toxicity/biomedical effects of the Hazardous Substances Data Bank, National Library of Medicine

Toxicity summary
Toxic hazard rating
Antidote & emergency treatment
Medical surveillance
Toxicity excerpts
Human toxicity excerpts
Nonhuman toxicity excerpts
Toxicity values
Human toxicity values
Nonhuman toxicity values
Ecotoxicity values
Minimum fatal dose level
Populations at special risk
Pharmacokinetics
Absorption, distribution and excretion
Metabolism/metabolites
Biological half-life
Mechanism of action
Interactions

These records contain 140 different data elements, grouped into ten categories.

The information used in an HSDB record is selected from secondary sources such as standard reference books, handbooks, criteria documents, and monographs and is supplemented with information from other on-line databases, such as TOXLINE, etc. The data extracted from secondary sources are reviewed quarterly by a scientific review panel (SRP) of experts convened by the NLM. Members of the SRP are professional toxicologists, industrial hygienists, and environmental engineers from academia or industry. Additional information from pertinent literature (secondary or primary and consensus statement) may be selected/developed by the SRP

Data extracted from secondary sources are reviewed quarterly by a scientific review panel.

and incorporated into an HSDB record to ensure that the record contains the most relevant and accurate information known today. Readers can obtain further information on HSDB or TOXNET by contacting Specialized Information Service, Toxicology Information Program, National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894.

The U.S. Air Force Installation Restoration Toxicology Guide

The Toxicology Guide was sponsored by the U.S. Air Force. A collaborative effort with the Harry G. Armstrong Aerospace Medical Research Laboratory at Wright-Patterson Air Force Base resulted in five, peer-reviewed volumes, written and compiled by technical staff of the Biomedical and Environmental Information Analysis Section of the Health and Safety Research Division of Oak Ridge National Laboratory.

One of the objectives of the U.S. Air Force Installation Restoration Program (IRP) is to provide individuals responsible for the management and implementation of the IRP with information to evaluate the health hazards associated with actual or potential contamination of drinking water supplies. Volumes 1 through 4 of the U.S. Air Force IRP Toxicology Guide contain information on 70 chemicals and complex mixtures of environmental concern to the U.S. Air Force. Volume 5 of the IRP Toxicology Guide contains similar information on seven metals and over 80 environmentally significant compounds containing these metals. Data summary sections providing concise, easily accessible data useful to environmental engineers precede detailed environmental and toxicological review sections. These summaries include chemical names and synonyms, registry numbers; physicochemical data; information on reactivity and handling precautions; soil-water persistence; pathways of exposure; health hazard data; environmental standards and criteria; and state, federal, and European Economic Community regulatory status.

The toxicology review sections for each chemical in the IRP Toxicology Guide include detailed information on acute, subchronic, and chronic toxicity data, as well as information on developmental toxicity, genotoxicity, and carcinogenicity. Environmental information for each chemical encompasses environmental fate and exposure pathways and fate and transport in soil/groundwater. A section on biological monitoring for each metal-containing compound is included. Compounds were included in this volume based on production volume and usage, existing regulatory concern for the specific compound, and the available toxicologic data.

Information on the U.S. Air Force IRP Toxicology Guide may be obtained from: Harry G. Armstrong Aerospace Medical Research Laboratory, Human Systems Division, Wright-Patterson AFB, OH 45433-6573, or Biomedical and Environmental Information Analysis, Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6050.

One of the objectives is to evaluate the health hazards associated with actural or potential contamination of drinking water supplies.

The toxicology review sections include detailed information on acute, subchronic, and chronic toxicity data, as well as information on developmental toxicity, genotoxicity, and carcinogenicity.

Teratology/Developmental Toxicology

No specific evaluated or peer-reviewed database for teratology or developmental toxicology comparable with those for genetic toxicology or carcinogenicity is available by which individuals can access test results on specific agents. There is a clear and urgent need for a value-added database for teratology or reproductive and developmental toxicology that is structurally similar to the Gene-Tox database. Until this happens, individuals who need to access evaluated data from these areas of research will have to rely on review articles, books, IARC Monographs, or the primary literature.

Summary and Conclusion

With today's high-tech communications systems saturating us daily with enormous amounts of information from around the world, it is very easy to suffer from information overload. We find ourselves struggling with the questions of how to interpret information. What does it mean for us? What should we do about it? How do we discern high-quality from lesser-quality information? Particularly in the scientific arena, the daily production of data is enormous and the need for high-quality data is greater than ever to answer such questions as, How do we extrapolate animal data for human application? and How do we conduct a valid predictive study?

Evaluated data should be the basis of predictive scientific efforts and must be a part of any database building/maintenance effort. We have addressed the issue of evaluated data and information resources for the field of toxicology, specifically for three of its major components — genetic toxicology, carcinogenicity, and teratology. ORNL, through development of specialized value-added information systems, is contributing significantly to the process of providing knowledge bases for specific toxicological disciplines by addressing the problem of duplication of effort and the saving of resources (such as time and money). Unfortunately, because funds for the maintenance of these databases have been reduced, the ability to make factual health risk assessments is in jeopardy. Those who need access to reliable data/information must ensure that funding for the development of specialized (value-added and peer-reviewed) databases and/or information files is proportional to that allocated for research. Table 5 lists key resources that we recommend for use in accessing toxicology information.

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Table 5. Recommended sources[a] for accessing the toxicology literature

Genetic toxicology

Recommended source for access to primary literature

Environmental Mutagen Information Center files available through the National Library of Medicine's (NLM) TOXNET system (74,000 records). This file covers literature published from 1968-1991

Recommended source for evaluated (peer-review) data

a. Gene-Tox through NLM's TOXNET system (4600 chemicals)
b. International Agency for Research on Cancer Monograph, Supplement 7, 1987 (950 chemicals)
c. Hazardous Substances Data Bank (4200 chemicals)

Teratology/reproductive/developmental toxicology

Recommended source for access to primary literature

Environmental Teratology Information Center files available through the NLM TOXNET system for literature published from 1950-1987 (46,000 records); literature published since 1988 may be obtained from NLM's Developmental and Reproductive Toxicology file, also available on TOXNET

Recommended source for evaluated (peer-review) data

Although several books and monographs are available summarizing experiments, no comprehensive peer-reviewed computerized database is publicly available currently (through 1990). However, selected studies that derive health risk assessment parameters are compiled by the U.S. Environmental Protection Agency's (EPA) Office of Health and Environmental Assessment's Chemical Unit Record Estimates Database. Currently, this is an internal EPA file

Carcinogenicity

Recommended source for access to primary literature

No specific information file devoted solely to this area of research is available. Bibliographic information is found scattered throughout numerous biological-oriented information files

Recommended source for evaluated (peer-review) data

a. International Agency for Research on Cancer monograph (52 volumes covering over 960 chemicals)
b. Gene-Tox database available through the NLM TOXNET system (392 chemicals)

General toxicology

Recommended source for access to primary literature

NLM's TOXLINE and TOXLIT systems

Recommended source for evaluated (peer-review) data

a. Hazardous Substances Data Bank available through the NLM TOXNET system
b. U.S. Air Force Installation Restoration Toxicology Guide, available through DTIC No. Vol. 1: ADA219797, Vol. 2: ADA214999, Vol. 3: ADA215001, Vol. 4: ADA 215002, and Vol. 5: ADA 238093 (Volumes 1-4 covers 70 organic chemicals and Volume 5 covers 6 metals with 87 environmentally significant metal-containing compounds)

[a]For an explanation of the information files, databases, or computer systems referred to in this table, see Table 1.

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EPA and the Federal Technology Transfer Act: Opportunity Knocks

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In 1986, the Federal Technology Transfer Act (FTTA) was established to promote a closer, collaborative relationship between federal government agencies and the private sector. With the increasing need for new cost-effective technologies to prevent and control pollution, both the U.S. Environmental Protection Agency (EPA) and private industry are encouraged to facilitate the transfer of knowledge and technology under this Act. The FTTA removed several of the legal and institutional barriers to cooperative research that existed before the Act's passage. Through the FTTA, the government strives to promote the movement of its products, processes, skills, and knowledge into the private sector for further development and commercialization by encouraging the exchange of technical personnel and the sharing of facilities and other resources. Collaborative efforts between industry, federal agencies, and academia are made possible through cooperative research and development agreements (CRADAs). Forty-two CRADAs and five licensing agreements have been initiated with EPA under this program. This paper provides an overview of this new and innovative program within the EPA.

Introduction

Both federal agencies and the private sector find an increasing need for new cost-effective technologies to prevent and control pollution. In the past, however, legal and institutional barriers have prevented government and industry from collaborating in the development and marketing of these technologies. The FTTA 1986 (P.L. 99-502) established a program designed to promote a closer, collaborative relationship between federal government agencies and the private sector. Under the FTTA, each governmental agency that conducts research is encouraged to facilitate the transfer of knowledge and technology to the private sector. In the EPA, the Office of Research and Development's (ORD) Office of Technology Transfer and Regulatory Support (OTTRS) is responsible for implementing the FTTA. Innovative technologies may flow in either direction between the government and the private sector. EPA's FTTA program recognizes that exciting and innovative research is being performed in private, as well as agency laboratories. Through the FTTA, the governmen' strives to promote the movement of its products, processes, skills, and knowledge into the private sector for further development and commercialization by encouraging the exchange of technical personnel and the sharing of facilities and other resources. By permitting the pooling of resources with industry, universities, foundations (profit and nonprofit), and other federal, state, and local governmental agencies, the federal government is seeking to overcome many of the barriers that have impeded the development and commercialization of federally-developed, innovative technologies in the past.

Through the FTTA, the government strives to promote the movement of its products, processes, skills, and knowledge into the private sector for further development and commercialization by encouraging the exchange of technical personnel and the sharing of facilities and other resources.

Participation in the FTTA program can benefit many parties and allow the private sector to become more competitive in both domestic and international markets. The FTTA has encouraged federal laboratories to assess the scientific and commercial potential of their ongoing and planned projects to determine whether a private sector organization might be interested in entering into a collaborative effort. The collaboration, which may involve the conception and/or development of an idea or invention, is usually formalized by the signing of a CRADA. CRADAs are one of the primary mechanisms through which the exchange of information and technology takes place under the FTTA. CRADAs often contain provisions regarding licensing of the final product. Licensing of an innovative technology may take place independently of a CRADA in accordance with the Bayh-Dole Act of 1980 and the FTTA.

Federal Technology Transfer Act

Since its inception, EPA's mission has been to protect human health and the environment. No other department or agency of the federal government has this function as a primary mandate. As an institution, EPA is largely concerned with fulfilling regulatory functions that have been mandated by federal legislation. The EPA FTTA program is based primarily on three pieces of legislation and two executive orders:

- The Stevenson-Wydler Technology Innovation Act of 1980.
- The Bayh-Dole Act of 1980.
- The Federal Technology Transfer Act of 1986.
- Executive Order 12591, April 10, 1987, as amended by Executive Order 12618, December 22, 1987.

The Stevenson-Wydler Act required all federal agencies conducting research and development to include technology transfer in their mission. It also required federal agencies to establish an Office of Research and Technology Applications to identify technologies and ideas with potential applications in other settings. The Bayh-Dole Act permitted government-owned laboratories to grant exclusive licenses to patents and permitted universities, nonprofit, and small businesses to obtain titles to inventions developed with government support. The third statute, the Federal Technology Transfer Act of 1986 amended the Stevenson-Wydler Act and empowered federal agencies to give their laboratory directors authority to enter into CRADAs. The CRADA could include advance agreements on title and license to inventions resulting from the CRADA. FTTA also required that a significant portion of license royalties be paid to federal laboratories and their employee inventors whether the invention came out of a CRADA or was licensed using the procedure of the Bayh-Dole Act. The FTTA also promotes collaboration between federal agencies and government-operated laboratories and other government and nongovernment entities. The primary mechanism through which such collaboration takes place, the CRADA,

The FTTA has encouraged federal laboratories to assess the scientific and commercial potential of their ongoing and planned projects to determine whether a private sector organization might be interested in entering into a collaborative effort.

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was established by the FTTA. Executive Order 12591, as amended by 12618, reiterates the purpose and goals of the FTTA.

Scenarios of Technology Transfer

Under EPA's FTTA program, co-development of technologies by government and the private sector can take place in a variety of ways. For example, technologies developed entirely in EPA laboratories can be transferred to the private sector for further development and/or commercialization. Also, technologies conceived or developed in the private sector may be further developed or improved upon jointly by EPA and the cooperator using EPA and cooperator personnel, equipment, and facilities if the development work is within the mission of the laboratory. Likewise, technology co-developed by both the government and the private sector can be further developed and commercialized by private industry.

In each of these scenarios, the EPA and the cooperator could enter into a CRADA, which would set forth the terms of the collaboration. The CRADA is an adaptable document; the specific terms will vary with each collaborative effort. For example, EPA may share technical expertise, facilities, equipment, supplies, or any combination thereof, with the cooperator. The cooperator may provide the same resources to the government, and also has the option of providing direct funding to a particular project. The government, however, is not permitted to provide direct funding to the cooperator.

FTTA Agreements

EPA has been entering into cooperative agreements with other agencies and organizations for years. These cooperative agreements have been a prime funding vehicle between EPA's ORD laboratories and nonprofit organizations. However, CRADAs authorized by FTTA are an entirely new kind of cooperative agreement.

A CRADA is an agreement that provides a written and legal framework for collaborative efforts between federal laboratories and private sector cooperators. CRADAs are one of the primary mechanisms through which collaboration between the government and the private sector takes place under the FTTA. As previously mentioned, CRADAs permit EPA Laboratory/Office Directors to pool resources with state and local governments, universities, and private industry to develop or to extend federally funded technologies to the commercial marketplace. In addition, a concept or technology that a cooperator originates may be developed or extended through the use of a CRADA.

Under the Bayh-Dole Act, EPA may also enter into licensing agreements for the commercial marketing of independently developed, federally-owned technologies. The licensing activity is primarily a business activity and the final, written record is a legal document called a licensing agreement. A license represents a contractual business relationship between a seller (EPA), who authorizes a buyer to use the seller's invention or intellectual

Under EPA's FTTA program, co-development of technologies by government and the private sector can take place in a variety of ways.

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property rights. Most often in the commercial arena, this transfer of intellectual property rights is for financial gain. Whether a licensing agreement evolves from a CRADA or from independently developed federally-owned technologies, FTTA requires the return of royalties to the laboratories for technology transfer activities, and to the inventors.

Advantages to CRADAs

There are many advantages to industry in signing a CRADA or licensing agreement. These agreements make possible the sharing of technical expertise, equipment, facilities and supplies. Under EPA's FTTA program, however, the overriding goal is the development and application of environmentally-beneficial products and technologies.

CRADAs provide the following advantages:

- Access to high-quality science through EPA's 12 research laboratories. Many of these laboratories offer an attractive combination of world-class personnel with state-of-the-art equipment and fully permitted facilities.
- Expanded working relationships between EPA and the private sector. Interaction between the two parties provides a stronger knowledge base for problem solving capabilities during technology development.
- Exclusive agreements for developing new technologies. Companies, under some CRADAs, are given exclusive rights to market and commercialize new technologies developed through joint research.
- Agreement flexibility. CRADAs are flexible enough to fit the goals of many different sizes and types of companies.
- Decentralized structure. The FTTA gives authority to Laboratory/Office Directors for administering the program. This accelerates the agreement process.

Current Program Information

Since 1989, EPA's FTTA program has been expanding rapidly. To date, 42 CRADAs and 5 licensing agreements have been signed. Tables 1 and 2 are lists of the present participants. The list of agreements includes the lead laboratory within EPA, the cooperator and a brief description of the technology being transferred. Currently, approximately 25 CRADAs and 5 licensing agreements are in negotiations.

A variety of organizations participate in this program. Participants encompass a broad range of organizations from private industry, academia, and trade associations. Figure 1 represents the types of organizations working with us. The majority of participants are small and large size businesses.

FTTA and the Future

As we look ahead at the economic growth within our nation, there is a need for stability and competitiveness. Many companies are faced with the lack of

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As we look ahead at the economic growth within our nation, there is a need for stability and competitiveness. Many companies are faced with the lack of resources, such as scientific expertise in a particular field, or highly specialized equipment.

Table 1. Signed FTTA Agreements—U.S. EPA Cooperative Research and Development Agreements (CRADAs)

Office/Lab	Cooperator	Technology/Purpose of CRADA
ORD/HQ	Exxon Corporation, USA	Development and demonstration of the feasibility of accelerating the rate of biodegradation of oil spill residues on Alaskan Shores
ORD/OEETD/AEERL	ABB FLAKT, Inc.	Development of absorbents for air pollution control technology
ORD/OEETD/AEERL	Aladdin Steel Products, Inc.	Further the development and commercialization of an EPA-patent for gas-enhanced woodstove technology for reducing emissions into the atmosphere
ORD/OEETD/AEERL	Nalco Fuel Tech, L.P.	Determining the sulfur dioxide and nitrogen removal efficiency by the EPA-patented calcium-based and urea-based sorbents
ORD/OEETD/AEERL	Nalco Fuel Tech, L.P.	Development of a combination Selective Catalytic Reduction/Selective Non-Catalytic Reduction process for nitrogen oxides emissions in combustion effluent
ORD/OEETD/RREL	Chapman, Inc.	Use of EPA's mobile in-situ soil containment technology for treating hazardous wastes
ORD/OEETD/RREL	Cold Jet, Inc.	Evaluate dry ice particle blasting and other abatement processes for the removal of lead paint
ORD/OEETD/RREL	Drysdale and Associates, Inc.	Development and evaluation of automatic sensors and data acquisition equipment for drinking water treatment plants
ORD/OEETD/RREL	Levine-Fricke, Inc.	Lab and pilot scale study of biodetoxification waste treatment technology for degrading solid
ORD/OEETD/RREL	Lewis Publishers, Inc./CRC Press, Inc.	Development of a cost and performance model for safe drinking water clean-up technologies
ORD/OEETD/RREL	Vulcan Iron Works, Inc.	Use of EPA's mobile incinerator for destruction of hazardous wastes
ORD/OEETD/RREL	Water Quality Association	Evaluation of a home water softener on the corrosiveness of water
ORD/OEPER/CORVALLIS-ERL	Niagara Mohawk Power Company	Use of a Biological Earthworm Assay to evaluate the efficiency of a thermal desorption technique
ORD/OEPER/RSKERL	Coastal Remediation Company	Development of bioremediation process to remove alkylbenzene contamination through injection into subsurface of a nutrient mix
ORD/OEPER/GULF BREEZE, FL-ERL	Electric Power Research Institute	Identification of a bioremediation technique to remediate mercury contaminated freshwater environments
ORD/OEPER/GULF BREEZE, FL-ERL	Southern Bioproducts, Inc.	Development of microbial isolates to degrade toxic chemicals
ORD/OEPER/GULF BREEZE, FL-ERL	Southern Bioproducts, Inc.	Performance of research on bioremediation of wood treatment waste sites
ORD/OHR/HERL	E.I. DuPont de Nemours and Company	Visual function research testing of a mixture of aliphatic dibasic esters
ORD/OHR/HERL	Pathology Associates, Inc.	Use of the SENCAR Mouse Assay for identifying complex mixtures in drinking water treatment plants
ORD/OHR/HERL	Spiral Systems Instruments, Inc.	Development and utilization of automated and semi-automated microbial mutagenicity assays
ORD/OMMSQA/AREAL	Autoclave Engineers, Inc.	Development and/or improvement of methods that use programmable pyrolysis for the analysis of trace organic species that occur in a condensed or other phase in the atmospheric environment
ORD/OMMSQA/AREAL	Dow Corning Corporation	Investigation of environmental effects on damage to coatings and sealants used on automotive products
ORD/OMMSQA/AREAL	Ford Motor Company	Use of EPA's Environmental Chamber Facility for evaluating effects of environmental fallout on automotive products
ORD/OMMSQA/AREAL	Frandon Enterprises, Inc.	Development of a test kit method for lead
ORD/OMMSQA/AREAL	Georgia Institute of Technology	Hydraulic model study for improved ocean outfall design at Boston Harbor
ORD/OMMSQA/AREAL	NuTech Corporation	Design, development, production, and testing of automated gas chromatographic injection equipment to determine organic compounds in ambient air

(continued)

Table 1. Signed FTTA Agreements—U.S. EPA Cooperative Research and Development Agreements (CRADAs)

Office/Lab	Cooperator	Technology/Purpose of CRADA
ORD/OMMSQA/AREAL	Perkin-Elmer Corporation	Development and improvement of physical and chemical methods for trace contaminant analysis, automated canisters sampling for gaseous contaminants, and diffusion monitoring technologies
ORD/OMMSQA/AREAL	Rohm & Haas Company	Paint substrate exposure study using covering-spray devices
ORD/OMMSQA/EMSL-CI	American Water Works Association Research Foundation	Biotechnology and tissue culture methods for monitoring viruses in ground water
ORD/OMMSQA/EMSL-CI	Fisher-Scientific Company and R.T. Corporation	R&D of solid matrix quality control samples
ORD/OMMSQA/EMSL-CI	NSI Technologies, Inc.	R&D of liquid organic standards and preparation, verification, distribution, and stability of these samples
ORD/OMMSQA/EMSL-CI	Perkin-Elmer Corporation	Development of sampling methods for the PCR technology
ORD/OMMSQA/EMSL-CI	Spex, Inc.	R&D of inorganic reference materials and preparation, verification, distribution, and stability of these materials
ORD/OMMSQA/EMSL-CI	Supelco, Inc.	R&D of liquid organic standards and preparation, verification, distribution, and stability of these samples
ORD/OMMSQA/EMSL-CI	Ultra Scientific, Inc.	R&D of organic reference materials and preparation, verification, distribution, and stability of these samples
ORD/OMMSQA/EMSL-LV	Dow Corning Corporation	Use of EPA's Indoor Air Chamber to test a Dow-developed instrument
ORD/OMMSQA/EMSL-LV	Fiber Chem, Inc.	Development of fiber optic chemical sensors
ORD/OMMSQA/EMSL-LV	Hewlett-Packard Company	Development of advanced laboratory instrumentation for exposure analysis
OAR/NVFEL & ORD/OMMSQA/AREAL	US CAR Env. Res. Consortium (Ford, GM, Chrysler, Navistar) and State of CA	Develop new technology to identify evaporative emissions and hard-to-detect low-level exhaust emissions from cars and trucks
OSWER/OUST	In-Situ, Inc.	Development of a field method for testing soil and water for VOCs
OSWER/OUST OEETD/RREL	Shell Oil Company	Evaluation of vacuum extraction technology for USTs
OW/OGWDW/TSD	CH2M Hill Southeast, Inc.	Use of EPA mobile packed column air stripping technology for treating drinking water contaminants

Table 2. Signed FTTA Agreements—U.S. EPA LICENSING AGREEMENTS

Office/Lab	Cooperator	Technology
ORD/OEETD/AEERL	ABB FLAKT, Inc./University of Texas	Licensing of absorbents for air pollution control technology
ORD/OEETD/AEERL	GenLime Group, L.P.	Licensing of Limestone Injection Multistage Burner process for reducing sulfur emission from coal plants
ORD/OEETD/RREL	Boyle Engineering, Inc.	Licensing of EPA patent on butylamine group-containing ion exchange resins for water purification
ORD/OEPER/Athens	Bio-Rad Laboratories, Inc.	Licensing of method for interfacing between a liquid chromatograph and a mass spectrometer for conditioning liquid stream from the chromatograph to the spectrometer
ORD/OEPER/GBERL	SBP Technologies, Inc.	Licensing of two EPA-patents on biological remediation of creosote- and similarly-contaminated soil and ground water

resources, such as scientific expertise in a particular field or highly specialized equipment. Partnerships among industry, academia, and the federal government bridge the gap between the market oriented private sector and the environmental protection prospective of EPA. Industry often lacks resources, such as time and money, for the development of new technologies. This, in turn, may impede or inhibit the development of a viable technology. If the U.S. is to become more competitive internationally, our industries, universities, and the federal government must join forces and work together toward a common goal. The FTTA permits speed in development and commercialization of innovative technologies. In our changing world and economy, this is crucial to our economic growth and stability.

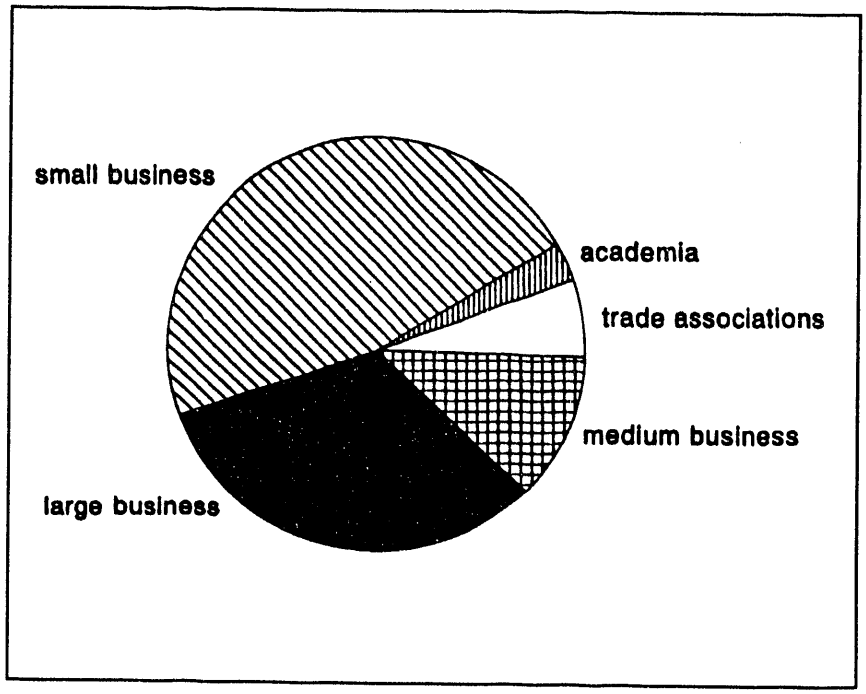

Fig. 1. Types of FTTA agreement cooperators.

Information Resources for Assessing Health Effects From Chemical Exposure: Office of Pesticides Programs

Penelope Fenner-Crisp, U.S. Environmental Protection Agency

The U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs is trying to develop a complete picture of a chemical's toxicity and exposure profile. It is also important to share information in the office's files because pesticides, particularly as a consequence of agricultural use, find their way into places not necessarily intended.

FIFRA 88 refers to the last time major amendments were made to the Federal Insecticide, Fungicide, and Rodenticide Act. FIFRA 88 contains some significant directives for the Environmental Protection Agency (EPA). Over the last 20 years, Congress has asked EPA to re-register all pesticides that had been registered prior to November 1984. Re-registration was attempted in 1972 and 1976, both times with meager results. In 1988 Congress "asked" again, but this time mechanisms were included to acquire financial support for resources. They also gave a time frame in which to accomplish this task; it must be complete by 1997. This means we must identify the data gaps that are inadequately filled. It also means that registrants of pesticide products will have to generate new data as appropriate. The agency then must review these new data and provide an opinion regarding the validity of the data with respect to continuing registration of the product. We started out with about 800 active ingredients but now are down to close to half of that, fewer than expected based upon preliminary evaluations.

The room next to my EPA office contains the world's mother lode of toxicology data: the largest database in the world on human health effects of pesticides. My colleague, Anne Barton, has the same sort of information available to her on environmental fate and ecological effects. I think the only other database that might closely compare in size is that of the World Health Organization's Expert Panel, which derives Acceptable Daily Intakes for pesticides. This is part of the work of the Joint Meeting on Pesticide Residues in cooperation with the Food and Agricultural Organization in recommending Maximum Residue Limits (international food tolerances) to Codex Alimentarius Commission.

You would think that all of this information ought to be more than enough for the Program to make decisions with respect to the registration, re-registration or cancellation of the uses of a pesticide. Generally, the Office has had a relatively parochial attitude on that point. Little information

We must identify the data gaps that are inadequately filled.

The largest database in the world on human health effects of pesticides is located at EPA.

in addition to the industry-sponsored data has been considered and integrated into our risk assessments and regulatory decisions. This practice may be satisfactory for registration purposes because usually, there are few data available from outside sources on the new(er) chemicals. However, the re-registration process covers only those pesticides registered before 1984. The Special Review process, which may lead to the banning or cancellation of a chemical, also tends to focus on older chemicals; thus, additional information on these is likely to exist. We receive many new studies during the course of re-registration and we often must ask for new data in the Special Review process. Even so, to conduct a high-quality risk assessment we must consider not just the sponsor's data, but also information on the chemical from other sources as well as data on agents in the same chemical class to use for structure activity analysis.

It is important that we develop a complete picture of a chemical's toxicity and exposure profile. I see it as a challenge to us in the Office of Pesticide Programs to make use of the many data bases described during the last few days. I have been aware of them, and during the year I have been in the Office of Pesticide Programs, I have prompted interest in them among my co-workers. We are gathering this information for incorporation into the database comprised of data submitted to us by the registrants. It is also important, as the law permits, for us to share information in our files with the rest of you because pesticides, particularly as a consequence of their agricultural use, find their way into places not necessarily intended. We also find them at waste sites such as Superfund sites. We find them as a result of agricultural run-off in our surface waters, and in groundwater, whether or not it is being used for drinking water. So, certainly other program offices in EPA and our sister Federal agencies, as well as the state and local governments, have significant interest in both the toxicity and environmental fate of pesticides. We hope to soon provide that information to you in a more expanded manner than we have in the past, and we can gather from you the information you may have collected, particularly on exposure, to assist us in developing sound regulatory decisions.

The Special Review process, which may lead to the banning or cancellation of a chemical, tends to focus on older chemicals.

It is important for us to share information in our files because pesticides find their way into places not necessarily intended.

Air Risk Information Support Center

Chon R. Shoaf and Daniel J. Guth, U.S. Environmental Protection Agency

The Air Risk Information Support Center (Air RISC) was initiated in early 1988 by the U.S. Environmental Protection Agency's (EPA) Office of Health and Environmental Assessment (OHEA) and the Office of Air Quality Planning and Standards (OAQPS) as a technology transfer effort that would focus on providing information to state and local environmental agencies and to EPA Regional Offices in the areas of health, risk, and exposure assessment for toxic air pollutants. Technical information is fostered and disseminated by Air RISCs three primary activities: (1) a "hotline," (2) quick turn-around technical assistance projects, and (3) general technical guidance projects.

Introduction

In 1985, EPA announced its National Air Toxics Strategy, which included provision of technical assistance to state and local agencies; Air RISC is a formal mechanism for provision of this assistance (Guth and Victery 1989). Air RISC is managed by a steering committee composed of 6 voting members from OAQPS, 5 voting members from OHEA, 1 voting member from the Center for Environmental Research Information, and 1 advisory member each from the Health Effects Research Laboratories, state and local agencies, regional offices, and the EPA library. The steering committee chairperson is rotated yearly between the Environmental Criteria and Assessment Office at the Research Triangle Park (ECAO-RTP) and OAQPS.

Technical information is fostered and disseminated by Air RISCs three primary activities: (1) a "hotline," (2) quick turn-around technical assistance projects, and (3) general technical guidance projects. The "hotline" provides inquirers with quick responses on health effects and risk assessment questions as well as needs for quick turn-around technical assistance projects. The Air RISC "hotline" is also a database for general technical guidance projects. Quick turn-around technical assistance projects are usually more limited in their scope of health effects and exposure population. General technical guidance projects include a wide variety of activities in risk assessment, risk communication, and training.

Technical information is fostered and disseminated by Air RISC's three primary activities.

"Hotline"

The Air RISC "hotline" provides an initial quick response to inquiries from state and local agencies and EPA Regional Offices. Responses are based on health and exposure information available through the expertise of Air RISC staff, resources (documents, databases, and library), and contractors. Experts in a variety of areas can answer questions from the caller directly or provide the appropriate information resources. Calls may also be referred to other EPA staff members with the appropriate expertise. The "hotline" operates Monday through Thursday from 8:00 a.m. to 5:00 p.m. and

Responses are based on health and exposure information available through the expertise of Air RISC staff, resources (documents, databases, and library), and contractors.

Friday from 8:00 a.m. to 4:00 p.m. Anyone on the staff of a local or state air pollution control agency or in the EPA Regional Office may make "hotline" inquiries.

"Hotline" calls are logged into a database by the receiving EPA staff member. Information stored includes the date of request; the staff member receiving the call; the requestor's name, address, affiliation, and phone number; the type (state, local, or federal) of call; the subject and pollutant of concern; the completion date; hours to complete; and an abstract of the call. The abstract includes a narrative description of the call along with pertinent names, telephone numbers, and copies of correspondence generated by the call. The database is used to store information and as an information resource. It can be used to save time and provide consistency when responding to similar requests. It is also used as a management tool for reviewing and reporting the status of Air RISC calls, description of clients which use Air RISC, the subject of calls, and time spent by EPA staff supporting Air RISC. Figure 1 shows the number of Air RISC cases by type from its inception to May 1990. During this period, scientists at OHEA and OAQPS responded to 1131 Air RISC calls from all sources. State agencies made the greatest use of the service. Local agency and EPA Regional Office use is about equal, but less than state agency use. Air RISC utilization by state over the same period is shown in Fig. 2. States with very active air pollution control efforts made more requests to Air RISC as indicated by higher numbers on the map. Seventy-three local

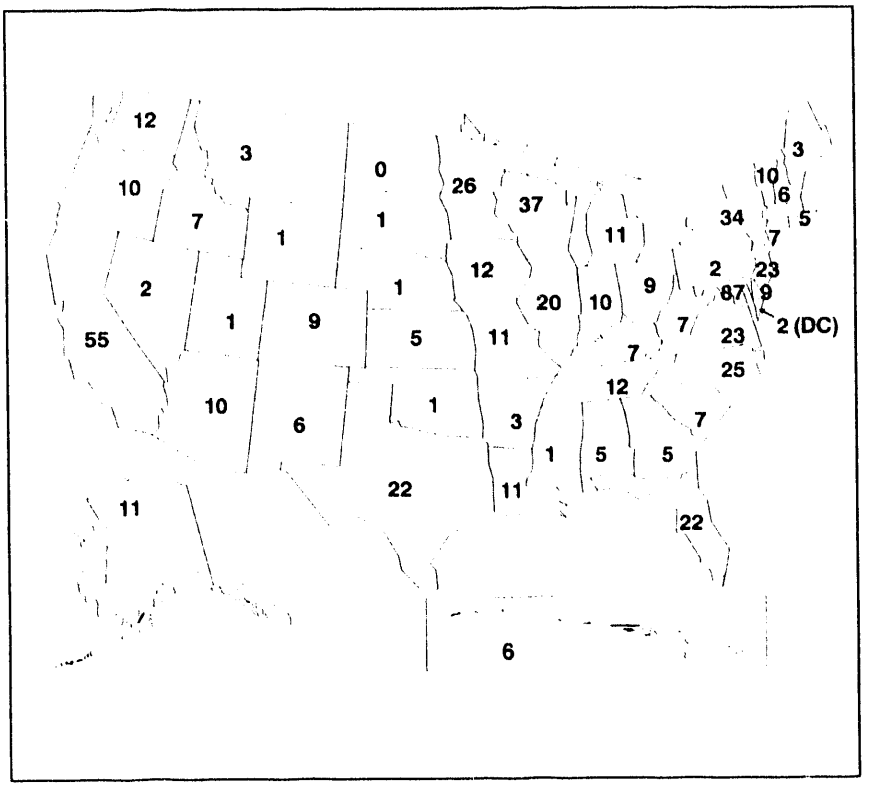

Fig. 1 Utilization of Air RISC by state agencies February 1988 through May 1990.

agencies from 25 states made inquiries of Air RISC. There were 1002 calls from state, local, and Regional Offices, representing 89% of the total calls. Thus, the clientele for Air RISC is largely, as intended, state and local agencies and EPA Regional Offices.

The greatest number of questions about single chemicals concerned dioxins, asbestos, benzene, styrene, formaldehyde, methylene chloride, chromium, hydrogen sulfide, arsenic, and mineral fibers. Questions regarding complex mixtures were asked most frequently, however. General questions on health effects, carcinogenic unit risk estimates, documents, or regulatory status were also asked frequently.

The "hotline" has identified various quick turn-around technical assistance projects needing completion, and the "hotline" data-

The greatest number of questions about single chemicals concerned dioxins, asbestos, benzene, styrene, formaldehyde, methylene chloride, chromium, hydrogen sulfide, arsenic, and mineral fibers.

base has been used to identify general technical guidance projects in health, exposure, and risk assessment that need to be addressed to meet the needs of the state, local, and Regional Office requestors (*inter alia*, tire burning and asphalt fumes).

Quick Turn-Around Technical Assistance

In some cases, an in-depth evaluation or retrieval of information may be more helpful than a rapid response. In such cases, detailed technical assistance projects may be required. If resources and time are adequate, such projects will be initiated. Technical assistance projects can be carried out in the following subject areas: assistance in understanding exposure and risk assessment methodologies; review and interpretation of toxicological literature; and review of site-specific exposure assessments, risk assessments, or both for adequacy of methods used and related interpretation features.

The Air RISC quick response project mechanism typically utilizes contractors when EPA staff are not available to do the necessary research or review. EPA staff then review the contractor's products. These projects are most often generated by "hotline" requests. The following is a list of some of the projects using quick response:

- Review of draft health impact protocol from incineration in Quincy, Massachusetts
- Comparison of upper bound confidence limit and maximum likelihood estimate
- Review of carbon disulfide document for Virginia

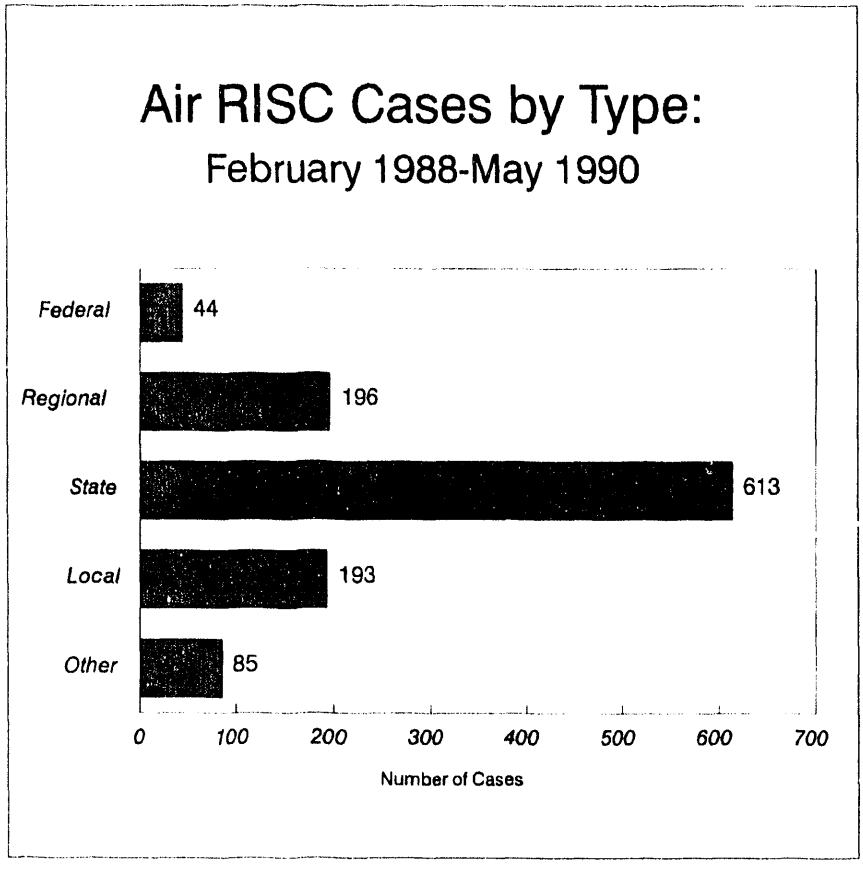

Fig. 2. Air RISC cases by type.

- Hexachlorobutadiene—health effects
- Triethylamine—health effects
- Coal dust—health effects
- Butyl cellusolve—health effects
- Review of aluminum facility health/risk assessment plan
- Review of toxicity of alkanes and alkenes
- Chemical carcinogenicity data from Kentucky Air Toxics Program
- Review of risk assessment work plan for point sources - Chattanooga, Hamilton County
- Review of exposure assessment portion of gasoline document

A list of some of the projects using quick response by Air RISC.

- Review of exposure assessment portion of gasoline document
- Review of New Hampshire method for deriving ambient air guidelines
- Summaries of toxicity data for 7 chemicals for Oregon State agency

General Technical Guidance Projects

The third major purpose of Air RISC is the completion of general technical guidance projects. These projects are of broad reaching toxicological, exposure, or risk assessment concern, and sometimes are performed with the joint collaboration and support of the Control Technology Center (CTC).

General technical guidance projects are of broad reaching toxicological, exposure, or risk assessment concern.

Air RISC and the CTC supported a project for the State of Florida's Department of Environmental Regulation on emissions and health effects of burning agricultural black plastic. Test burns, emission sampling, and simulated burnings were funded by CTC, and Air RISC funded the mutagenicity testing of the emissions by the Ames test. No mutagenic potential was found in the vapor or particulate emissions, but concentrated extracts of the particulate sample were moderately mutagenic. Mutagenic potential was similar to emissions from residential wood burning as determined from the literature.

Air RISC supported a project which reviewed the health effects of asphalt fumes. CTC provided information on asphalt production and emissions according to its use. The health effects of emitted chemicals were reviewed, but additional emissions data and dose-response relationships are needed.

Based on a request by Region 8, Air RISC performed a risk assessment pertaining to a steel mill in Utah. Joint participation by CTC involved characterization of emissions from integrated steel mills. A document describing the steel-making process, process stream emissions, and cancer and noncancer health effects of the emissions was prepared.

Air RISC is also involved in technical guidance projects such as producing a *Glossary of Terms Related to Health, Exposure, and Risk Assessment.* This document is a resource for state, local, and Regional Office personnel who deal with toxic air pollutants. A *Directory of Information Resources Related to Health, Exposure, and Risk Assessment of Air Toxics* was prepared by Air RISC to assist state, local, and Regional Office personnel. Air RISC also offered three-day workshops on risk assessment and risk communication for state and local air pollution control agency personnel. The workshops provided sessions on health and exposure assessment, toxicology, and risk assessment. More in-depth sessions cover pulmonary toxicology, inhalation reference concentration (RfC) methodology, noncancer risk assessment, pharmacokinetics, and the most recent agency concepts in cancer risk assessment. Important concepts in risk communication, such as public involvement, explanation of technical issues, risk perception, conducting public meetings, and dealing with the media were also

Workshops provided sessions on health and exposure assessment, toxicology, and risk assessment.

covered. Based on the premise that odor or sensory irritation may be related to pulmonary damage or damage to other organs, a project characterizing the odor threshold, sensory irritation, and critical target organ of several hundred air toxics was started by Air RISC.

A project to provide guidance to state and local air pollution officials who perform site-specific risk assessments for point sources is under way. Carcinogenic and noncarcinogenic risk assessment methodologies will be outlined with areas of conflict and unresolved differences in methodologies resolved by presentation of various options and resource requirements. Air RISC is also supporting a project that will provide guidance to agencies for including risk communication and public involvement as part of air toxics programs.

References

Guth, D. J., and W. Victery. 1989. Air Risk Information Support Center Status Report, February 1988-June 1989, U.S. Environmental Protection Agency, Air Risk Information Support Center, Research Triangle Park, North Carolina, EPA 450/3-89-32.

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Chemical Substructure Analysis in Toxicology

Robert O. Beauchamp, Jr., Center for Information on Toxicology and Environment

A preliminary examination of chemical-substructure analysis (CSA) demonstrates the effective use of the Chemical Abstracts compound connectivity file in conjunction with the bibliographic file for relating chemical structures to biological activity. The importance of considering the role of metabolic intermediates under a variety of conditions is illustrated, suggesting structures that should be examined that may exhibit potential activity. This CSA technique, which utilizes existing large files accessible with online personal computers, is recommended for use as another tool in examining chemicals and drugs.

Chemical Substructure Analysis (CSA) has become a highly sophisticated procedure as illustrated by its use in the field of toxicology and other biomedical disciplines. If a chemical, drug, or pesticide is modified during use or exposure, the intermediates become part of the analysis. For example, in pharmaceutical or toxicological research, chemicals are exposed to different kinds of biological media and may be subject to metabolic conversion. CSA techniques in toxicology are similar in many aspects to development of a novel drug in which a basic chemical structure of a known drug may be changed to yield a more active and efficacious product. Chemical structural features of test compounds may vary with functional groups, physical dimensions, hydropathicity, electrophilicity, nucleophilicity, or susceptibility to enzymatic modification, to mention a few. These are important features to consider where chemical bonds are disrupted and new structures formed that may bind to biological substrates such as proteins, by enzymatic coupling, oxidation-reduction reactions, or acid base equilibrium. Such alterations of the basic chemical structure can affect the biological activity. CSA may employ many technical disciplines including organic chemistry, medicinal chemistry, molecular modeling, pharmacology, biochemistry, pharmacokinetics, pathology, and veterinary and human medicine. Some of the principal benefits from CSA of test compounds under various experimental or environmental conditions are to (1) predict chemical conversion, (2) determine chemical reactions, (3) elucidate metabolism, and (4) relate chemical structure to biological activity.

Important chemical structural features should be considered where chemical bonds are disrupted and new structures formed that may bind to biological substrates such as proteins, by enzymatic coupling, oxidation- reduction reactions, or acid base equilibrium.

CHEMICAL SUBSTRUCTURE ANALYSES IN TOXICOLOGY

BENEFITS —

- PREDICT CHEMICAL CONVERSION
- DETERMINE CHEMICAL REACTIONS
- ELUCIDATE METABOLISM
- RELATE CHEMICAL STRUCTURE TO BIOLOGICAL ACTIVITY

Fig. 1. Benefits of chemical substructure analysis.

In the early analytical stages of CSA, after establishing the exact structure of the model test compound and any contaminants, the potential metabolic sequence should be delineated in order to focus on a set of chemical structures. If the metabolic sequence of the test compound has been established previously, the CSA can be directed to structures associated with the reported metabolites. Certain functional groups may be susceptible to "biomedical" modification and should be considered at this initial stage of CSA along with closely related chemical derivatives.

Computerized techniques have contributed greatly to the CSA process during the past decade. The chemical connectivity file compiled by the Chemical Abstracts Service (CAS) currently contains over 11 million records on reported substances. Incorporated into each record is the connectivity code for each compound in which every atom and its adjacent attachments can be searched singly or in multiple combinations (i.e., chemical substructures). This large chemical file is available online through the Scientific and Technical Information Network (STN) under the title—REGISTRY FILE (Reg file). The records in this file include not only single compounds but mixtures, salts, polymers, addition compounds, and coordination compounds. Each record contains Registry Numbers (RN), names, synonyms, molecular formulae, structural diagrams, and the total number of references that may be queried in the CAS bibliographic files. In addition, the Reg file can be searched for word fragments simultaneously in several index fields of the separate records along with the substructure searches giving the user a very powerful tool. The foregoing record fields that contain different terms can be utilized in preparation of a search statement. Terms may be utilized to broaden or narrow the search. Boolean logic can be applied to multiple terms to focus on a particular set of compounds.

After a set of chemical structure records is retrieved from these search queries in the Reg file, the records may be examined for cited structures to determine whether the compound search should be expanded or limited to specific structural configurations. The final chosen set of compounds from the Reg file can then be searched in a second bibliographic file also available on STN—CHEMICAL ABSTRACTS FILE (CA file) in which a particular activity such as metabolism or toxicology is searched for in abstracted publications.

The CA file contains the complete bibliographic record for publications abstracted by CA since about 1965 and contains approximately 5 million reference citations. The reference citations include author names, titles, document sources plus other searchable fields—document type, major subject sections (such as toxicology, pharmacology, etc.), publication year, language, abstract, keywords and index terms. Proximity term searching can be employed also in which search terms must be positioned either in the same index field or different fields and in a prescribed order. Boolean logic can be applied to the search

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terms in searching the CA file as with the Reg file. For example, a set of compounds (substructure set from Reg file) can be searched in the CA file and the separate bibliographic references queried for specific biological activity such as inhalation toxicity in the rat.

Before performing a CSA search of the computer files, selection of the chemical substructures based on the "parent" compound should be carried out according to the following general procedure.

Step 1 —

Test compound: Examine the compound for chemical class (e.g., amine, acid, alcohol, or epoxide), potential for biotransformation or metabolism (e.g., enzymatic reduction/oxidation, or coupling), reactivity with substrates (e.g, water, DNA, or peptides), and bonding characteristics (e.g., covalent, H-bonding, pi bonding, or van der Waals).

Test compound intermediates: Modify the chemical structure of the test compound according to reported metabolic data or probable conversion products based on analyses in the first step. The complete structure of test compound can be entered in the Reg file and modified by either addition or deletion of chemical fragments. Starting with the original compound has the advantage of visually following the conversion steps. Also, this approach focuses on the points of attachment or chemical change and usually includes a larger portion of the test compound, which potentially yields a smaller number of compounds in the substructure set.

Ultimate activity structure: Determine the probable chemical structure causing adverse effec or pharmacological action (may be final conjugated product excreted/released or an intermediate resulting from biotransformation, etc.).

Preliminary CSA Study

Phenylbutazone (PBZ), or butazolidine (Fig. 2), was selected as a prototype to illustrate the CSA procedure as outlined in the foregoing section. This drug has been used as an anti-inflammatory agent since the late 1940s. Many references are available in the open literature reporting its activity in various animal species and under a variety of conditions. Numerous variations in the basic chemical configuration of PBZ have been synthesized and tested for alteration in activity. Also, this drug was reviewed recently by the Peer Review Panel of the National Toxicology Program (NTP) Board of Scientific Counselors and Technical Reports Review

Phenylbutazone (PBZ), or butazolidine, was selected as a prototype to illustrate the CSA procedure as outlined in the foregoing section. This drug has been used as an anti-inflammatory agent since the late 1940s.

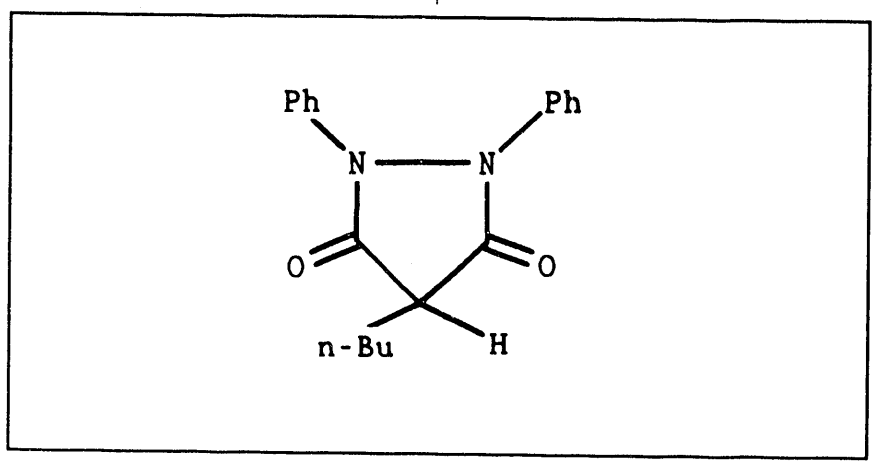

Fig. 2. Strucutre of phenylbutazone.

Subcommittee for its potential toxicity and carcinogenicity. Evaluation by the Peer Review Panel indicated the following conclusions from a 2-year bioassay gavage study with rats and mice (NTP 1990) :

1. Equivocal evidence of carcinogenic activity in male rats (F344/N)—renal cell adenomas and carcinomas.
2. Some evidence of carcinogenic activity in female rats (F344/N) —transitional cell carcinomas in kidney. Nephrotoxic to rats.
3. Some evidence of carcinogenic activity in male mice (B6C3F1)—increased incidence of hepatocellular adenomas and carcinomas.
4. No evidence of carcinogenicity in female mice (B6C3F1) at elevated exposures (150 or 300 mg/kg in corn oil).

These conclusions have been accepted relative to animal toxicity by the National Institute of Environmental Health Sciences (NIEHS) and were subsequently released in a NTP report (March 1990).

The chemical structure of PBZ is composed of a pyrazolidine heterocyclic ring that has been substituted in five positions. The heterocyclic ring contains two nitrogen atoms adjacent to each other in the 1- and 2- positions. Two unsubstituted phenyl groups are positioned at the 1- and 2- positions on the nitrogen atoms, two keto groups at 3- and 5- positions, and an alkyl straight C-chain (butyl) at the 4- position of the heterocyclic ring. PBZ may be synthesized by the reaction of 1,2-diphenylhydrazine and the n-butyl alpha-substituted malonic acid ester. In the CSA the chemical structures of the starting materials also should be considered for clues to metabolite structures and possible techniques for modifying the test compound.

The chemical structure of PBZ is composed of a pyrazolidine heterocyclic ring that has been substituted in five positions.

Metabolism of PBZ has been studied in numerous biological systems and the chemical sites associated with metabolic transformation have been noted. As yet, no particular metabolite has been designated as the putative structure associated with disclosed carcinogenicity. Toxic components of the test compound may be elucidated by blocking the reactive sites observed in the metabolism sequence or by administering large doses of a certain metabolite and observing any changes in toxicity. From the metabolic sequence data reported for PBZ, there are six principal reaction sites: (1) hydroxylation of the phenyl groups in the para-positions, (2) omega-1 oxidation of the butyl chain yielding a butanone or butanol, (3) omega-2 oxidation of the butyl chain forming a beta-hydroxybutane, (4) ring cleavage of the pyrazolidine ring between the 4- and 5- positions and subsequent formation of a lactone ring with the hydroxyl group of the butyl chain, (5) hydroxylation of the 4-position of the pyrazolidine ring, and (6) formation of glucuronides/sulfates at possible reactive sites. Depending on the biological conditions, it is possible for more than one of these metabolites to be present or even more than one reactive site to be modified simultaneously in the original parent compound.

From the metabolic sequence data reported for PBZ, there are six principal reaction sites.

From this metabolic information, the CSA is focused on certain chemical substructures for analysis of PBZ. Several of these substructures have been searched in the Reg file and then submitted to the CA file for possible biological activity. The following procedure is suggested as a model in conducting a CSA and relating structure to activity.

Two principal substructures of PBZ were selected for initial investigation. The first structure is symmetrical diphenylhydrazine in which definite atoms or substituents have been designated. This substructure represents ring cleavage of the pyrazolidinedione ring and retains the two phenyl groups on adjacent ring N-atoms. The phenyl groups may be substituted only in the para-position, as suggested by hydroxylation limited to these positions.

The second selected principal substructure consists of five- or six-membered 1,2-dinitrogen heterocyclic rings and phenyl groups on each of the ring N-atoms and keto groups on the heterocyclic rings adjacent to each of the ring N-atoms. The five-membered heterocyclic ring is a pyrazolidine-3,5-dione, and the six-membered heterocyclic ring is a pyridazine-3,6-dione. These two heterocyclic ring structures were queried separately in the computer Reg file to obtain sets of compounds possessing the desired chemical substructure characteristics. The sets were then queried in the activity file (CA file) to determine any reported toxic activities.

The STN system was entered through a computer terminal (IBM PC/XT) with a modem and the Reg file queried for the diphenylhyrazine (DPH) substructure. Registry numbers may be used to enter structures in the Reg file and then modified according to the desired structure. A sample search was performed with only 5% of the file, and this search projected 53 to 477 compounds in the full 10 million-compound file. A complete search gave 136 compounds. When this structure set was searched in the CA file, 492 references were found. This reference set was then restricted to the following word fragments: [mutat?, mutag?, carcino?, neoplas?, terato?, metaboli?, or DNA]. The total number 492 was reduced to 34 references. Figure 3 lists the three derivatives with indicated toxicity as derived from this search procedure.

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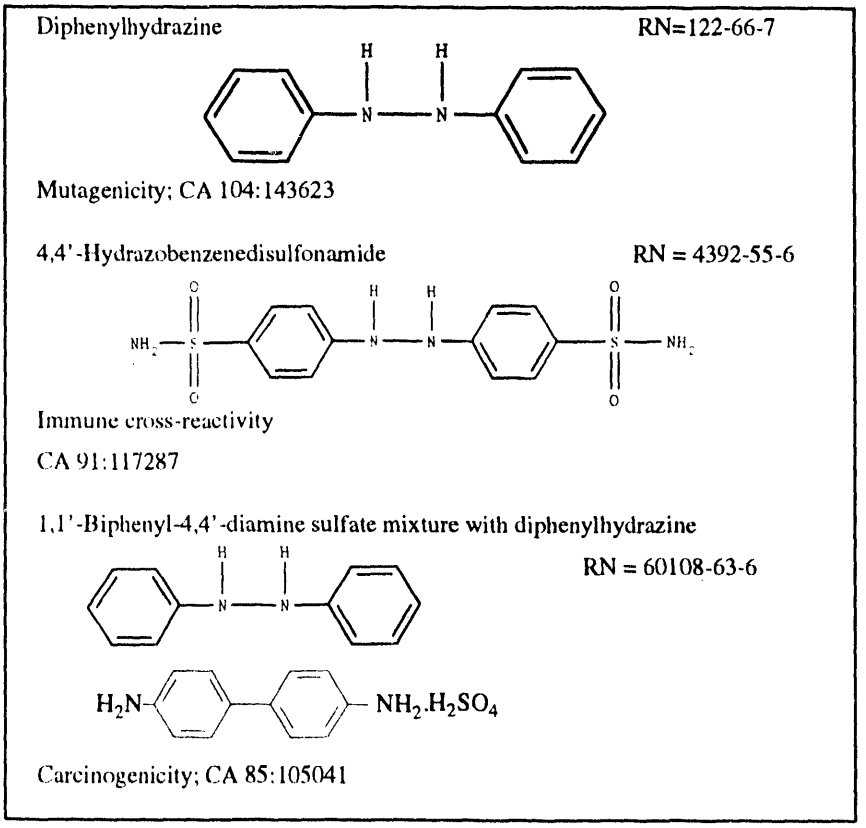
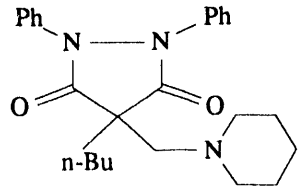


Fig. 3. DPH substructure derivatives and toxicity.

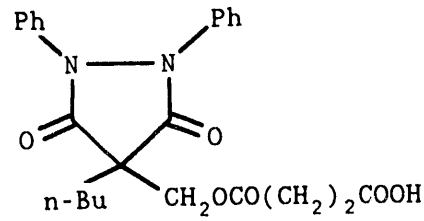
The second set of proposed chemical substructures was queried in the Reg file (i.e., pyrazolidinedione and pyridazinedione) and a set of 1355 compounds was obtained. PBZ was eliminated because it is not considered one of the substructures leaving 1354 derivatives. (References to toxicity of PBZ can be performed in a single search and should not be considered with the chemically modified components.) Searching this substructure set of 1354 compounds in the CA file gave 1769 references. This reference set was then limited to the following terms: carcino? neoplas? mutat? mutag? terato? DNA, metaboli? or genet?. Only 358 references were cited. Examination of this set of references indicated that only six derivatives (for pyrazolidinedione) were reported to be mutagenic. The structures for these derivatives are shown (Fig. 4).

In the course of this analysis, a novel software program entitled METABOLEXPERT (available from CompuDrug USA, Inc., P.O. Box 202078, Austin, TX 78720) was examined to determine whether metabolic sequences could be predicted based on similar reactions observed with structurally related compounds. Preliminary results are being examined with this novel approach, and it represents a general technique that may be useful in investigating metabolic sequences. Ouchi and Wipke (1978) used the program to predict metabolites of xenobiotic compounds. As more information is introduced into each of these computer systems, the probability increases of predicting metabolic transformation for a

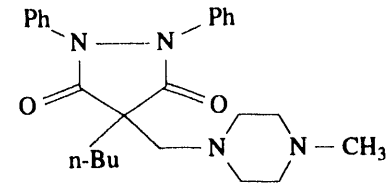
4-(Piperidinomethyl)phenylbutazone RN = 74152-34-4



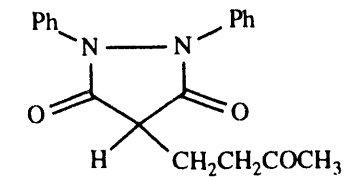
4-Hydroxymethylbutazolidine hemisuccinate RN = 27470-51-5



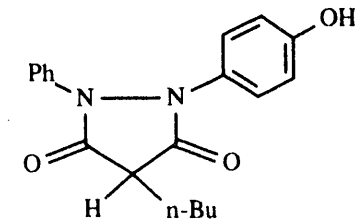
4-[(4-Methyl-1-piperazinyl)methyl]phenylbutazone RN = 27315-91-9



Ketophenylbutazone RN = 853-34-9



Oxyphenylbutazone RN = 129-20-4



1,2 Diphenyl-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione RN = 57-96-5

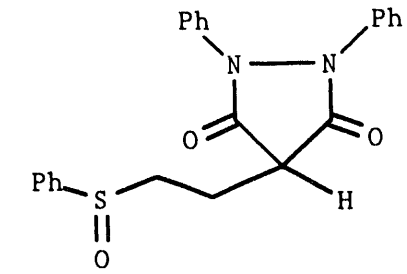


Fig. 4. Mutagenic pyrazolidinedione substructures.

candidate chemical. Such a system would be highly useful to the biochemist studying the pharmaceutical or environmental activity of compounds.

Summary

This preliminary examination of CSA has demonstrated the effective use of the Chemical Abstracts compound connectivity file in conjunction with the bibliographic file for relating chemical structures to biological activity. The importance of considering the role of metabolic intermediates under a variety of conditions was also illustrated, suggesting structures that should be examined that may exhibit potential activity. This CSA technique, which utilizes existing large files accessible with online personal computers, is recommended for use as another tool in examining chemicals and drugs.

Acknowledgment

The author wishes to express appreciation to the Chemical Industry Institute of Toxicology for support in the early stages of this study in evaluating the potential of CSA.

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Information Resources and the Correlation of Response Patterns Between Biological End Points

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and John S. Wassom, Oak Ridge National Laboratory

This paper focuses on the analysis of information for mutagenesis, a biological end point that is important in the overall process of assessing possible adverse health effects from chemical exposure.

From 1966 until 1972, John Wassom and I worked together in the Biology Division of the Oak Ridge National Laboratory (ORNL). In 1968, at the request of the Environmental Mutagen Society, we started the Environmental Mutagen Information Center (EMIC) that you have heard about during this meeting, especially at the poster session. Since I left Oak Ridge in 1972, my work has been such that I have not been directly involved with the problems associated with information management and use. This symposium has brought me back to Oak Ridge once again to talk and think about these issues and has been a pleasant homecoming for me.

In this short presentation, we would like to focus on the analysis of information on one specific biological end point that is important in the overall process of assessing possible adverse health effects from chemical exposure. This important end point is mutagenesis. Many people today use the broader term "genetic toxicology" to describe the research area that attempts to identify agents that induce genetic damage rather than "mutagenesis," but in this paper the old-fashioned term of "mutagenesis" will be used.

During the last 20 years, mutagenesis came to be known as the "little brother" of carcinogenesis. This particular relationship is especially true for the field of risk assessment. Mutagenesis has been mainly used during the last two decades as a diagnostic tool to predict the carcinogenic potential of agents, especially chemical agents. The majority of these short-term mutagenicity test systems have come and gone as they have fallen into disgrace and nonuse as a result of data that indicate the inability of these systems to function as predictive tools for identifying potential human carcinogenic agents. Scientists and health administrators sometimes get disillusioned when this happens because there is no quick and easy means to identify such hazards. We think, however, that when the issue of employment of mutagenicity assays to identify potential carcinogenic agents is put into historical perspective, it takes some of the edge off the disappointment.

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This paper gives a brief historical overview of short-term

mutagenesis test systems and the problems of (1) interpreting information obtained from them to correlate response patterns among them and (2) comparing these end points to other biological end points such as carcinogenesis. This historical perspective will be used to see where all this may lead in the future.

Short-term mutagenesis test systems come and go, as information available from the EMIC documents show. In John Wassom's talk, the creation of EMIC was correlated with high interest in the field of mutation research and the proliferation of assay systems developed for the purpose of identifying agents that induce genetic damage (Malling and Wassom 1977).

In 1968, John and I were asked to serve on the Mrak Commission that was formed to evaluate hazardous effects of pesticides. The formation of this commission marked one of the first serious attempts to assess the potential adverse health effects of a specific group of chemical agents. At that time, the need or importance of including metabolic activation as part of the experimental protocol for *in vitro* mutagenicity assays was not yet appreciated (although it was thought about) and the Ames/Salmonella microsome test system did not exist. Nevertheless, hundreds of compounds were being tested for genetic activity in a variety of easy-to-use systems. Prevalent among these early systems were two plant assays, *Allium cepa* and *Vicia faba*, that measure the ability of test agents to induce chromosome aberrations in root tips. These test systems were reasonably simple to do and were quick and inexpensive.

Today, with the literature and data compilation capabilities of EMIC, it would be easy to survey the literature for data on the mutagenicity of the pesticides being reviewed by the Mrak Commission. However, in the summer of 1968, EMIC was not in existence, so we found ourselves working long hours in a hotel room in New Jersey, reading the papers that had taken us so long to locate and copy for the purpose of summarizing the mutagenicity data on pesticides. Most of the data we reviewed were for pesticides evaluated in either the Allium or Vicia test. This large compendium was assembled without the aid of a computer. The tables that resulted from this review and evaluation effort served as the principal component of the Mrak Commission Report (1969). This laborious data analysis project led us to several conclusions. First and most important of all, it helped to solidify our thinking about the importance of our involvement in establishing an information and data gathering facility for the field of mutagenesis. EMIC was formally organized in 1969 at ORNL's Biology Division to serve the area of mutagenesis. Fortunately for the field of mutation research, this activity is still in operation today, 21 years later. Elizabeth Von Halle presented a poster about EMIC at this meeting. The Mrak Commission report also made it clear that the Allium and Vicia tests did not distinguish between the active or the inert ingredients of pesticide mixtures. This revelation contributed to the eventual fall from grace of these two test

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systems — which is somewhat similar to what has happened in more recent times with the Ames/Salmonella microsome system.

After the Allium and Vicia test systems failed to meet expectations, many other assay systems arrived on the scene; the most notable of these new test systems was the Ames/Salmonella microsome assay (Kier et al. 1986).

With this system, researchers and health administrators started to correlate the mutagenicity and carcinogenic activity of compounds by simple qualitative means by assigning each compound either a "+," "–," or a "+/–" to indicate its mutagenic and carcinogenic activity.

A little more sophistication was added to this type of comparative compilation when the degree of mutagenic activity for compounds was indicated by assigning them various numbers of "+"s according to their mutagenic potential. Needless to say, such compilations produced a highly subjective information base. It was soon learned that chemicals have different degrees of mutagenic specificity, some low and some very high. Even with the Ames/Salmonella microsome assay, investigators were finding chemicals that would induce quite a high level of mutations in one of the five standard test strains but not in the others. This observation led Dr. Bruce Ames, who developed this popular and widely used test system, to make the statement that *carcinogens are frameshift mutations*. This same specificity was noted in other mutagenesis assays and prompted other workers to make similar observations, including my own statement that *carcinogens mainly induce base-pair substitution mutations* that result in the production of changed but functional proteins (Malling and de Serres 1969).

Today, we know that both of these statements are still valid as examples of possible types of genetic events or mechanisms that may lead to the initiation of the carcinogenic process but they are not exclusive. There are many other mutagenic events that could be causative factors in the initiation and development of neoplastic growth. As a result of further research on the question of whether all mutagens are carcinogens, it was discovered that some carcinogens were not mutagenic at all. Even though this came as a surprise and disappointment to some, it is something that should have been expected (Malling and Chu 1974).

Why did we choose to use the simple method of using "+"s and "–"s to analyze data when we knew this method was limiting and when it was clear that we were not using all the available data? This was done because it was the only approach we knew that could be easily used with the information systems available at that time.

In 1979, 10 years after the formation of EMIC, a program supported by the U.S. Environmental Protection Agency was initiated that helped revolutionize our thinking about the usefulness of short-term mutagenicity test systems to predict carcinogenesis and to identify agents capable of inducing heritable genetic damage. This program

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came to be known as the Gene-Tox Program, or Gene-Tox for short, and this activity is ongoing (Waters 1979; Green and Auletta 1980; Waters and Auletta 1981; Ray et al. 1987). The extensive data collection and review effort of Gene-Tox provides a unique resource of peer-reviewed genetic toxicology test data on over 4600 chemicals evaluated in one or more of 73 short-term bioassays. These data can be utilized as a primary source of data/information for more in-depth analysis and review studies.

In 1979, a program was initiated that helped revolutionize our thinking about the usefulness of short-term mutagenicity test systems.

Out of the Gene-Tox Program came the idea of combining the "+"s and "–"s from different mutagenicity test systems to see what combinations correlated best with the carcinogenicity of a compound. This type of data analysis became rather convoluted, but something positive came out of it. It was found that by combining data from the Ames/*Salmonella* microsome assay and from the rodent micronucleus test, one could obtain the best battery for predicting carcinogenicity. Without Gene-Tox, such an observation would not have been possible.

During the last few years, several techniques have been proposed to aid in the review and analysis of biological test results. One such method was suggested by Dr. David Brusick (Brusick 1987), and Committee 1 of the International Commission for Protection against Environmental Mutagens and Carcinogens (ICPEMC) (Lohman et al. 1990). The thinking behind this proposed technique was that if each chemical under study was given an activity number that takes into consideration the different tests that have been performed with that chemical, then data analysis would be made easier and more systematic. It has been proposed that this activity number may be related to carcinogenic potency (Nesnow 1990).

Several techniques have been proposed to aid in the review and analysis of biological test results.

Another of the techniques proposed in the quest to obtain usable methods to enhance our ability to review and analyze data was developed by Waters and colleagues (Garrett et al. 1984, 1986; Waters et al. 1988a). This technique is called the graphical activity profile (GAP) method and provides a visual portrait of the genetic activity for a given chemical as a function of dose (Waters et al. 1988b). Dr. Michael Waters presented a paper on this method and "hands-on" experience with the GAP computer program was available during the poster session of this symposium. The graphical plotting of the lowest effective dose for each chemical with a positive response and the highest ineffective dose for chemicals with a negative response provides an easy means to depict test data individually for each test system. In this technique, there is no attempt to combine data from various test systems. In other words, this method does not mix apples and oranges. This system has one important feature—the data points used in plotting a chemical's activity profile is selected from a set of references obtained from the published literature, and these references are linked to the GAP data in an accompanying information file. This means that if the lowest effective dose used to generate the data point on the graph is questioned or if use of the initial

genotoxic rate per concentration unit is preferred, the original publication cited in the associated information file can be consulted and modifications made as necessary.

The mutagenicity of a chemical, as pointed out earlier, is sometimes used as an indicator for carcinogenicity, and one of the best ways to describe the mutagenicity of a chemical is through use of a pattern or profile that depicts the response of the chemical in various test systems. If a parallel system existed for carcinogenesis, we would not have to rely on "+" or "–" to analyze carcinogenicity data; we would be able to consider and think more intently about the patterns observed in the data. Some carcinogens have shown an increase in the incidence of tumors above the spontaneous level in one tissue, while at the same time showing a lower than spontaneous yield in another tissue or body site of the same animal. This feature is clearly evident in the carcinogenicity test data amassed by the National Toxicology Program (NTP). The NTP has rules for handling cases of this type in order to arrive at a "+" or "–" for the chemical being tested. If the technique to generate graphical activity profiles from carcinogenesis data were available to analyze the NTP data, it would not be necessary to have such rules when working with patterns or profiles. If we had the capability of generating such patterns of response for chemicals evaluated for carcinogenicity, we would be able to explore such questions as

1. What type of tumors were induced by these chemicals?
2. In what animals/strain/sex?
3. At what doses?
4. At what body site, etc.?

With this information we could also link carcinogenicity data with mutagenicity data that could be used to answer questions such as, What features and conditions characterize nongenotoxic carcinogens? and Which of these may trigger carcinogenic activity? Having answers to these questions could provide us the basis to formulate a workable carcinogenesis model.

With such a combined database, other questions could also be more adroitly pursued. Are there correlations between tumorigenic specificity with respect to strain, species, tissue, etc.? Are there correlations between the types of induced tumors and the pattern or mutagenicity for a specific chemical or class of chemicals?

One of the greatest challenges, with respect to making maximum use of the current information and data, is to have available the kind of data analysis tools that will allow the development of meaningful risk assessments. Currently, the GAP technique is one such tool that merits serious consideration for application to most areas of toxicology where the adverse effects of a chemical or class of chemicals are being reviewed and evaluated. It has been pleasing to learn at this symposium (in the poster by Elizabeth T. Owens et al.) about the application of the GAP methodology to the analysis of response patterns obtained with chemicals evaluated for the induction of developmental and/or reproductive toxicology end points. The initial results

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One of the greatest challenges is to have available the kind of data analysis tools that will allow the development of meaningful risk assessments.

from these studies are published in the journal *Teratology* (Kavlock et al. 1991).

As we look to the challenges of the future, more information will be generated and developed regarding the adverse health effects of chemicals. Toxicity data and other information from many different types of biological systems will become available including the accumulation of human health data. If we are going to make proper use of this data/information, then procedures that allow us to correlate biological activity patterns with human health protection must become a standard part of the risk assessment process. With such a capability, we may be able to learn much more about the animal models we are using and their applicability in human hazard assessment. The capability to study patterns in biological test data through, for example, a profile correlation system will give us the ability to investigate the exceptions that may be found in the data. In so doing, we will be able to focus on the more crucial experiments needed to determine the validity of a particular model before a lot of time and money are spent. Such capabilities can also be applied to increasing our knowledge of the underlying processes or causative factors responsible for initiating a specific type of toxicological event.

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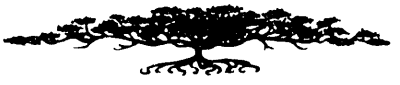

Information Resources for Assessing Health Effects From Chemical Exposure: Challenges, Priorities, and Future Issues

Sidney Siegel, National Library of Medicine

Issues related to developing information resources for assessing the health effects from chemical exposure include the question of how to address the individual political issues relevant to identifying and determining the timeliness, scientific credibility, and completeness of such kinds of information resources. One of the important ways for agencies to share information is through connection tables. This type of software is presently being used to build information products for some DHHS agencies. One of the challenges will be to convince vendors of data of the importance of trying to make data files available to communities that need them. In the future, information processing will be conducted with neural networks, object-oriented database management systems, and fuzzy-set technologies, and meta analysis techniques.

Over the 100 years that Quantitative Structure-Activity Relationships (QSARs) has been evolving, it has taken interesting shapes, forms, and directions. I would like to update your knowledge in this area so that you can consider when to apply these decision support methods and identify for you some information resources currently or soon to be in development. Two such resources are now being developed. One is a Directory of Risk Assessment Projects—sponsored or conducted by Department of Health and Human Services (DHHS) Agencies. Once this directory is up and running, it will be coordinated with an EPA-sponsored risk assessment compilation project.

The other project is an inventory of exposure-related data systems sponsored by federal agencies that will encompass the entire federal establishment and go as possible into state health and environment agencies. The challenge in putting such directories together is not limited by computer technology but the ability to address the individual political issues relevant to identifying and determining the timeliness, scientific credibility, and completeness (and thus, the usefulness for decision making) of information carried by such resources. In the not distant future we hope to present to the Committee to Coordinate Environmental Health and Related Programs (CCEHRP) Council a concept for the development and deployment of a directory of epidemiology research projects supported by DHHS. CCEHRP is under the DHHS Assistant Secretary.

Two resources are now in development: one is a Directory of Risk Assessment Projects, the other is a Directory of Exposure Information Resources.

Over the years, tens of millions of dollars have gone into epidemiology studies that have "slipped through the cracks" and thus, their usefulness is impossible to determine. Directories make it possible to share this information across the federal establishment and into the private sector. Appropriately structured, maintained and deployed

Over the years tens of millions of dollars have gone into epidemiology studies that have "slipped through the cracks."

directories will reduce duplication of such efforts.

We are all burdened with the necessity to handle the flow of huge amounts of data and information that come through our organizations because of our regulatory or scientific functions. One federal agency that I have been involved with over the last 2 years has been the Agency for Toxic Substances and Disease Registry (ATSDR). I first went to help them address their document and information management problems—one government person helping another government agency. At that time there was storage trailer after storage trailer of paper that had been generated that was relevant to the human health assessments done by ATSDR around National Priorities List (NPL) waste sites. I asked a simple question, "What's your disaster recovery procedure, if this stuff is destroyed?" The response was, "We don't have any." What I would like to describe briefly is an imaging system that they have since put into place, of which I will emphasize one component. The imaging system can efficiently and effectively capture all ATSDR relevant information onto optical disk through use of laser scanning technology —no matter what kind of paper it is on, no matter what the font. The available optical disk capture technology makes this easy. The special feature of this module of their HAZDAT system is that it contains font independent software that allows any frame on the optical disk to be selected and translated into the machine format required by most word processing software packages. Right now there is a significant cost for the software modules that comprise the ATSDR imaging system. But the capabilities are intriguing, they advance the state-of-the-art, and should be studied for their potential usefulness to other organizations.

The imaging system can efficiently and effectively capture information from documents relevant to ATSDR.

I would like to give you some history related to what we have been dancing around over the last couple of days—the ability to accomplish structure or substructure searches. Before Bill Farland was at EPA, Linda and some of the participants here for this symposium were at EPA. At that time we had some interesting negotiations and dialogue with Chemical Abstracts Service (CAS) concerning federal use of CAS information files and the CAS connection tables. At one meeting which was getting no where, one of us at the table, to break the impasse, turned to Dale Baker, the head of CAS, and said, "What we should seriously consider doing is nationalizing the CAS Registry system". Well, you should have seen the look on his face; it was interesting. Not long after that Marilyn Bracken, the Deputy General Council of EPA, and I ended up in the congressional office of a representative of the state of Ohio and were asked to explain why we were trying to destroy a particular organization in Columbus, Ohio. The remainder of that exchange was interesting. At that time we were not able to make use of CAS connection tables in any cost-effective way. Now the world has moved on and some elegant, standardized software is available that can build connection tables which are not CAS dependent. Technically, many of us are now going in this direction. The use of connection

Such systems are intriguing, advance the state-of-the-art, and should be studied for their potential usefulness.

tables descriptive of chemical structures will be one important way for us to share information across federal, state, and private sector organizations as means to more precisely identify data useful in decision making . We are now using this type of software to build information products for some of the DHHS agencies. I think that is going to be an increasingly important means of management support for many of us.

I have also mentioned over the last few days my interest in numeric files that can be derived from toxicologic experimentation. If anything is going to increase the efficient and effective accomplishment of the assessment or management of risk it will be the capability to efficiently identify relevant numbers which are derived from standardized toxicity evaluation procedures—numbers on which reasonable bounds can be placed as to their timeliness and credibility. Experiments have been done that show that building such files is simply a production-line problem. The challenge will be to convince vendors of information of the importance of making this kind of data file available to communities that need it. Once numbers are available, it is possible to begin to identify and understand the use of various kinds of models applicable to analysis of the data. In the past we haven't had the capability to identify and exchange models relevant to addressing various scientific problems or to develop forums to help us better understand the usefulness of a model, including bounding interpretation of results derived from application of the model. These approaches are possible now. Some of the things that we heard about joint ventures with the private sector should be seriously considered. These approaches are important because the application of models to actual human and environmental health problems will be a significant part of the decision-making efforts in the future. There is no need to go in and reinvent the infamous wheel. As a matter of fact, one of the Greek philosophers several thousand years ago said, "If we do not make use of the information of past ages, the world will remain in infancy." There is no need to remain in infancy now, because we have the technical capability to share information and to study the data of other investigators. In the past, decision-making has made heavy use of what is called delphitic techniques. In this approach, a group of experts sit around a table and hassle each other to arrive at a consensus decision that is reasonable. Too often, the decision may be based on the strength of personalities within the group rather than on relevant data. We would like to get you interested in helping us evolve machine-readable files relevant to the "mechanism of action" of chemical agents in biological systems and to biological markers which indicate effects that may be induced or superseded by exogenous agents. We need to show how these files of data, and information relate to one other and efficiently and effectively support decision making. At the poster sessions you saw the application of computer-based technology called expert systems. Expert systems are just the very first blush of what will be coming. Here, you saw vari-

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Joint ventures with the private sector should be seriously considered. These approaches are important because the application of models to actual human and environmental health problems will be a significant part of the decision making process in the future.

ous versions of relational data base management systems, including Hypertext. In the not distant future, we will be able to apply information processing means called "neural networking" and"object-oriented DBMS," "fuzzy-set" technologies, and "meta analysis techniques." The ability to sort the information and to talk about the probability of what the results will mean will be dependent on the scientific expertise that is, in part, here in this room. The future is within our grasp. Let's not get bogged down in a semantic swamp. Instead, let's talk about which way to go from here.

Let's not get bogged down in a semantic swamp.

Concluding Remarks: Where Do We Go From Here?

William H. Farland, U.S. Environmental Protection Agency

Where do we go from here in terms of access and use of information resources in assessing health risks from chemical exposure? We will need to look at new applications of relevant information available to programs at the federal, regional, and state levels and try to develop additional hands-on tools that will allow all of us to do our jobs. The application of available information to program decision-making and to risk management is one of the most important things that confronts us.

These concluding remarks will address the question, "Where do we go from here in terms of access and use of information resources in assessing health risks from chemical exposure?" We have dealt with this topic for the past two and a half days. First, we learned that, because science and risk assessment are evolving, we need to look toward the future. We will need to look at new applications of the relevant information available to programs at the federal, regional, and state levels and try to develop important additional hands-on tools that will allow all of us to do our jobs. The application of available information to program decision-making and to risk management is one of the most important things that confronts us. To a certain extent, we have a perspective based on what we have learned from this meeting, a perspective that suggests we must proceed. Before we proceed, however, there are a few questions that must be asked. One of these is, "Where do we go from here?" We have talked about where 'here' is over the last few days, but I want to give you my personal perspective of where 'here' is.

Characterizing the state of the field in information sciences is not simple; it's an issue that we face all the time. We have a tremendous amount of information, we have the scientific community with which to interact, we have the regulatory decision-making process, and we have the public with whom we have to communicate our decisions and policies. We have to let them know what information we have, what information we don't have, and the way that we have taken information availability into account in our decision-making process. We have to deal with the challenges, the priorities, and the future issues regarding information access and use.

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With regard to priorities, one thing I think is most important, which we heard discussed in detail yesterday, is the importance of the timeliness of the data. How are we going to be able to keep up with the information that is being generated out there in the scientific community, and how are we going to get it into a form that we can use? What kinds of time sensitivities

Importance of the timeliness of the data.

are we going to build into the databases so that we make use of the most current information? Use of the most current information in our decision-making process is the only way we are going to get the scientific community to stand behind us or support our decisions. What are some of the priorities and priority-setting mechanisms we might use to determine the type of information that ought to be evaluated and included in databases? This whole issue of timeliness and quality of information is an extremely important priority for us in terms of the future.

Speed and ease of access to information has been characterized over the course of this symposium: user friendliness and advances in hardware and software to facilitate dealing with the quality and quantity of information. One of the things that I am often told by people in the field is that they would like to see improvements in the portability of information systems. In other words, they would like to be able to have the information system accessible to them in the field or on-site via portable hardware. These perspectives are going to be extremely important as we begin to deal with access and use of information in the future.

In the most recent sessions, we have talked about enhanced analytical capabilities and the importance of combining these capabilities in new ways to evaluate the patterns that might emerge once we have adequately looked at particular topics of interest. We must also be looking to use such an approach to supplement our evaluations of chemicals or other agents for which a tremendous amount of information is not available at this point.

Another important question with regard to analytic capability is how should we actually express and understand uncertainty in the work we do? How can we evaluate databases to understand the uncertainty inherent in specific decisions?

During this symposium, we have heard about different approaches to risk assessment that included looking at new biological end points. The fields of neurotoxicology, immunotoxicology, and ecological effects, in general, are going to be areas we will have to include in the risk assessment process. To do this, we are going to have to develop new databases or new approaches to databases. In addition, we are looking toward various ways to quantify our risk assessments both in these new areas as well as in some of the older areas. New approaches for quantifying data will be needed, and the usefulness and acceptance of these approaches will depend on being able to go back to the original data and evaluate the impact of the newer approaches and compare them with current approaches.

Will the new approaches facilitate improved risk assessment? Will concepts such as reference doses or plausible upper bounds on risks still be used? Will the information make better or best estimates of risk possible in the future? What will the output of these approaches to these assessments look like? These questions are particularly important to consider in both the short and long term in regard to the access and

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The advances being made in science create a challenge for the future. We have enough trouble dealing with information as it comes out today. The new and different types of scientific information being produced very often don't fit our current risk assessment paradigms nor do they necessarily fit our current approaches to database management or development. Scientific advances are to some extent driven by the better and more efficient use of the available information and through development of better risk assessment models, but the new information that results often increases the uncertainties of these assessments and models.

Clearly, the expanding information bases are going to be important. John Wassom spoke about the trends in scientific publications that should be taken into account. For example, in the genetic toxicology literature the frequency of publications peaks in the mid-1980s and then drops off. How should such a trend be considered in making decisions about what information to use to build databases, and how should such trends be tracked? What journals should be included in databases? What information should be looked at, and how are limitations in our information systems to be explained to users once these kinds of decisions have been made? Although we don't often access the European information base, it may be useful to do so as we evaluate data and the expanded databases available.

In looking at such systems as the Integrated Risk Information System (IRIS), the Chemical Unit Record Estimates (CURE) database, and other systems that have been available during this symposium, it is evident that some critical decisions are needed regarding what kinds of information would be most useful. How much is enough? What amount of information is pertinent to users, and what amount overloads systems to such an extent that people will not use them simply because there is too much material for them to read or too much analysis left for them to do? As information specialists, we must deal with the expanding information base and the level of sophistication necessary to make the system an effective tool. This question pertains both to the level of the tools and the transfer of the resultant products. This is technology transfer as it relates to training in information management, in risk assessment, and in concepts of risk communication—some of the things discussed here over the last few days.

Critical decisions are needed regarding what kinds of information would be most useful. How much is enough?

This type of meeting provides a rare forum for discussion. The ability to talk with others and share experiences is useful. However, symposia end. We need to find ways to share the experience among an increasingly sophisticated user group. For example, we need to avoid reinventing the wheel on site-specific assessments. Even though these activities are 'site-specific' and should be carried out by local agencies, a tremendous amount of information is contained in those site-specific assessments, and many of the elements have broader application. How do we get this

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type of information out? The issue here is not only communication to the scientific community, which is experienced to some extent with our databases, but also how these databases can be used in dealing with the public.

One of the things that came up in Linda Tuxen's talk was the fact that EPA had initially made a conscious decision to develop IRIS as an internal database so that the agency could better interact with the external community. As the agency has been extended, stretching its limits by decentralizing risk assessment and providing more information to the public, these tools also had to be extended. However, the tools were not designed to provide information that is ready to be handed directly over to the public; the current tools would be confusing to the public and, in a lot of cases would be, if not discouraging, perhaps misleading to the public. It is important, then, to understand how to use these tools and how to communicate better, not only with the scientific community, but also with the public—not giving the half-answers that they often hear about what risk assessment can do. We need to be more skilled in dealing with the available information and somehow move toward an understanding of the uncertainties in the information so that we can deal with the public in a really straightforward manner about the risks or hazards that might be identified from the available information. Again, this is a real challenge.

We have talked about the concept of the feedback between the risk assessment process and the research in the information management community. Such feedback helps information managers to determine what needs to be done in terms of research, data collection, or data management to support the risk assessment process. This will continue to be an issue in the future. The question on this particular issue is, "From whom do we take our signals?" How do we determine the critical data needs? How do we factor what we have heard from our state and federal colleagues here? How do we identify those critical data needs and bring them to bear in terms of information management and then, eventually, risk assessment?

How do we identify those critical data needs and bring them to bear in terms of information management and then risk assessment?

The end of our panel discussion led very nicely into this discussion of changing technology because one of the things that I wanted to mention was the optical disk, or CD-ROM, approach to management of information. We are looking at this within my own program in a number of areas—in some cases just to make our own documents more readily available to us. Currently, many of the exposure assessments that have been done over the years in the Exposure Assessment Group are being captured on CD-ROM. This technology will be extremely useful in terms of accessing that information and providing it to people to use as an exposure-assessment library. We hope that we will be able to do that with more of our documents. In addition to that, we have talked about putting the IRIS system on this type of a database along with other types of information that could be used as a companion to IRIS (e.g., risk assessment guidelines when they come out and risk communica-

The optical disk, or CD-ROM, approach to management of information is being developed.

tion information). These things will be very useful to us in terms of disseminating information and making the information more usable to decision makers. In addition to this, a real advance has been demonstrated at this meeting with regard to changing technology, in terms of both software and hardware for data management. However, just about the time we get comfortable with one system, someone comes along with a new and better one. The systems we are using now will be outmoded or obsolete in the future. Somehow, we have to plan for this evolution as we project future data management and use.

Leveraged funding is extremely important. We must spread the burden of support for the types of things that we have been talking about—access and use of information, experience, etc.—over as broad a base as we can. This means that we have to look at new ways of leveraging. We have to look at experienced information/research centers and determine how we can generate the necessary revenue to keep them going. We don't want to lose the databases that have been developed over time simply because the newness has worn off. We have to be in a position to use the types of tools that you heard about this morning. The Federal Technology Transfer Act (FTTA) initiative has provided a good opportunity for us to think about some new ways to leverage funding. In my own program, we have had an opportunity to address this with regard to information collection; if we can build a strong enough case in information management and use, we will also be able to bring in some of this funding. In the next few days, we will be talking with our senior agency officials about a Chemical Manufactures Association initiative to determine what role industry might have in both supporting and helping us with the critical review of some of the information that goes into the IRIS system. This represents an extension of and increased participation by the user community, which is recognizing the value of these types of tools. We hope that over time this will lead to funding.

We must spread the burden of support over a broader base by looking at some new ways to leverage funding.

The final issue, in terms of the future, is public perception. The public perception issue is not just one of public perception of risk assessment, but public perception of the scientific community and its ability to deal with the current problems that are facing the public. This is important in terms of our ability (1) to reach consensus on issues and disseminate information that is particularly useful to the communities that need to make hard decisions with regard to the public and (2) to instill some confidence in the public that the information that they use is the best that's available (i.e., information that will be widely supported by scientists). One of the most discouraging things that can happen in terms of public perception is when the public hears divergent opinion about a risk issue. A scientist from the EPA, for instance, makes a statement about a particular issue, and then the public hears another well-respected scientist taking a very different position on the issue and the public just doesn't understand who to believe. How do we go about trying to get consensus positions developed? Although I am not

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particularly afraid of getting consensus around a position that may not be absolutely the best or absolutely right, I am concerned that we don't stifle information by just trying to present a unified approach to the public. That is something that we need to look at in the terms of future issues.

The question of whether or not we can continue to make progress in this field will depend on public perception of our ability to use the information that they have paid for and to make the right kinds of decisions with regard to risks. If we lose the public confidence with regard to either of those two points, we are going to lose the potential of having risk assessment be a driving force in decisions. Decisions will be made for other reasons—as, for instance, some of the congressional initiatives that have been developed. It is a real fear for us in terms of the future, but it is something that we can deal with.

These are some of my personal thoughts with regard to some of the priorities and challenges and future issues I see with respect to information use and access. I personally have found this meeting to be extremely beneficial; I think that most of the people who have talked with me over the last couple of days have also found it useful.

I would like to take just a moment to thank the Organizing Committee again for putting this meeting together, particularly the Biomedical and Environmental Information Analysis Section staff at the Oak Ridge National Laboratory who worked so hard to make this meeting a success. In addition, I think it is important for us to recognize the people who manned the posters and the demonstration sessions, because I believe that these were some of the most important parts of this meeting. These sessions gave us the opportunity to try some new things and do some hands-on work. I do not want to leave out the speakers and the other participants for their efforts in making the symposium a success. As you no doubt hear from my remarks, the answer to the question, "Where do we go from here," will depend on you.

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1

Biomedical and Environmental Information Analysis Section: Computing Resources

Sherry C. Campbell, Roswitha T. Haas, Donald G. Kilgore, and Kathy C. Miller,
Oak Ridge National Laboratory

The Biomedical and Environmental Information Analysis (BEIA) Section has a wide variety of resources available for its computing tasks. The section owns several processors which are networked on a Local Area Vax Cluster. These machines include a VAX 3500, a VAX 3100, a MicroVAX II, and a VAX 11/785. The in-house software includes ORACLE and BASISplus database management systems (DBMS) and FOCUS, a fourth-generation programming language. Additionally, BEIA relies heavily on PCs and has developed applications that use spreadsheets, database managers, expert system shells, desktop publishing software, CAD/CAM software, and computer graphics software. The BEIA resources are also linked to the central Martin Marietta Energy Systems, Inc., computing resources, which include a whole gamut of processors currently available from high-end VAXs to IBM mainframes to the Cray supercomputer. Plans are also being developed for obtaining a massively parallel processor for use in developing applications in the area of large full-text database processing. The software available on these resources, which can be used primarily for information technology problems, includes DBMSs such as DB2, INQUIRE, ENTERPRISE, and SYSTEM 1032.

2

Application of Expert System Shells to the Areas of Health, Safety, and Environmental Accountability

Kathy C. Miller, Roswitha T. Haas, Donald G. Kilgore, and Helen A. Pfuderer,
Oak Ridge National Laboratory

An expert, or knowledge-based, system consists of two basic parts: the expertise or knowledge, which is contained in some form of rule set, and the inference engine, which contains the computer instructions that guide the reasoning or chaining process through the rule base. Additional peripherals may be incorporated into the application, including databases, spreadsheets, report generators, electronic forms, text processors, etc.

The Martin Marietta Energy Systems, Inc., (Energy Systems) Expert Systems Education and Application Development Team has developed several expert systems relating to human health, safety, and environmental accountability. These include the NEPA Environmental Review and Compliance Reporting System, the RCRA/TSCA Advisor, and the Air Permits Expert System.

The NEPA Environmental Review and Compliance Reporting System is an expert advisor that assists in the preparation of documentation for compliance with National Environmental Protection Act (NEPA) require-

2 *continued* . . . . . .

ments, as well as other Department of Energy (DOE) and Oak Ridge National Laboratory (ORNL) standards, e.g., Best Management Practices Standards, as they apply to activity efforts at ORNL.

The RCRA/TSCA Advisor is designed to be used both as a computer-based instruction tool for training in compliance issues based on the Resource Conservation Recovery Act (RCRA) and the Toxic Substances Control Act (TSCA) and as a field-deployed advisor on these issues in actual work environments at Energy Systems.

The Air Permits Expert Systems is designed to generate accurate, reproducible, uniform air permit applications, which are then electronically delivered to the Division of Air Pollution Control, Department of Health and Environment, State of Tennessee.

Another system, the Project Quality Assurance Plan Advisor, which is in development, will address the environmental issues of concern to DOE, the Environmental Protection Agency, and others as projects are planned and completed at Energy Systems.

3 . . . . . .

ROADMAPS to Information Sources on EPCRA Section 313 (TRI) Chemicals

John S. Leitzke and James F. Darr, U.S. Environmental Protection Agency

ROADMAPS is a database that directs people interested in Emergency Planning and Community Right-to-Know Act (also known as SARA Title III) Sect. 313 (Toxic Release Inventory) data to additional information. The first part of the database allows searching by specific chemicals for information on cancer, health and environmental effects, federal regulations, general information documents, and state air and water regulations and monitoring information. Other parts of the database allow searching for chemicals by type of information. Bring a high-density formatted diskette to obtain a copy of the program.

HARDWARE: IBM-AT or 286-based or compatible PC.

SOFTWARE: MS-DOS 2.1 or greater, 12 KB RAM or greater.

4 . . . . . .

EPA/OTS Information Resources

Linda A. Travers, U.S. Environmental Protection Agency

The U.S. Environmental Protection Agency (EPA) Office of Toxic Substances has many information products and databases that are utilized in assessing health risks from chemical exposure. The poster presentation will highlight two of these databases: GEMS (Geographical Exposure Modeling System) and TRI (Toxic Release Inventory).

4 *continued*

GEMS is an interactive computer system developed to support integrated exposure assessments. It provides a set of tools without requiring the user to be familiar with most aspects of computer science and programming. GEMS integrates graphics, mapping, statistics, file management, modeling, and chemical property estimation with a user-oriented and easy-to-learn interface.

TRI is a publicly accessible database mandated by Congress in SARA, Title III or the Emergency Planning and Community Right to Know Act of 1986. It contains an annual inventory of releases of specified toxic chemicals to all environmental media (air, water, land). TRI is available on the National Library of Medicine's TOXNET system and is searchable using both user friendly menu screens and direct command line language. EPA was directed to make the inventory available either through computer telecommunications or via other means. The other means products include CD-ROM, COMfiche, magnetic tape, and floppy disks. All of these products are available through NTIS or GPO.

5

Dose-Duration Plot

Christopher H. Cubbison, U.S. Environmental Protection Agency

D2PLOT is designed to plot the results of dissimilar experiments in a common format of dose and exposure duration. This permits comparison of studies using a variety of species, exposure durations, dosing scenarios, and other variables. Details of dose and duration are entered on the data base along with extensive data on the toxicological endpoints, target organs, number of animals tested, number of animals responding, quality of data, bibliographic information, and comments. Data are searchable on all fields except comments. Results are plotted by Human Equivalent Duration (fraction of a human lifespan) vs. Human Equivalent Dose (mg/kg) for oral exposure or Expanded Concentration Scale (mg/m^3) for inhalation exposure. The type and severity of effects are indicated by the data points. Optionally, the software will plot boundary lines which encompass all adverse effects (Adverse Effects Region) and all no-effect-levels (No-Adverse-Effects Region). Areas outside these regions indicate where no data exist. Overlap between regions constitutes a Region of Ambiguity. Guidelines for use of the identified "regions" are under development.

6

Toxicology Information Response Center: Customized Information Acquisition

Kimberly G. Slusher, Mary W. Francis, and Ida C. Miller, Oak Ridge National Laboratory

The Toxicology Information Response Center (TIRC) serves as a national and international center for the collection, analysis, and dissemination of toxicology-related information on a variety of chemicals, including food additives, pharmaceuticals, industrial chemicals, environmental pollutants, heavy metals, and pesticides. We also have the capability of designing, building, and maintaining customized databases and writing and publishing reports. TIRC is sponsored by the National Library of Medicine.

7 . . . . . .

The U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS)

Linda Tuxen and Jacqueline Patterson, U.S. Environmental Protection Agency

The Integrated Risk Information System (IRIS), developed by the U.S. Environmental Protection Agency (EPA), contains summary information related to human health risk assessment. IRIS, which is updated monthly, is the agency's primary vehicle for communication of chronic health hazard information that represents EPA consensus positions following comprehensive review by intra-agency work groups. It is a useful information resource tool that points the user to the underlying human and/or animal data used to support the agency's consensus opinion. IRIS contains chemical-specific information in summary format for over 400 chemicals and provides a description of the basis for the hazard assessment and a discussion of the uncertainties in that assessment. An IRIS chemical file is initiated when consensus is reached on an assessment for carcinogenic or noncarcinogenic end points and contains the summary for that assessment. Other information, such as drinking water health advisories and EPA regulatory actions, is included. IRIS is primarily intended to provide guidance to EPA personnel in making risk management decisions. However, in 1988 it was made available to the public and can currently be accessed via several different methods: telecommunications link with a commercial carrier (BT Tymnet), through the Public Health Network to Public Health Foundation members, on the National Library of Medicine's TOXNET system, and on diskettes from the National Technical Information Service (NTIS). For more information on IRIS, contact IRIS User Support at 513-569-7254 or write IRIS User Support, ECAO/EPA (MS-114), 26 West Martin Luther King Drive, Cincinnati, Ohio 45268.

8 . . . . . .

Graphical Activity Profiles in Genetic Toxicology and Developmental Teratology

Elizabeth T. Owens, Oak Ridge National Laboratory, and T. Owens Vaughan, H. Frank Stack, Marcus A. Jackson, Robert J. Kavlock, and Michael D. Waters, U.S. Environmental Protection Agency

For many years two specialized information centers, the Environmental Mutagen Information Center (EMIC) and the Environmental Teratology Information Center (ETIC), have provided easy access to information available in the fields of genetic and developmental toxicology. Because of information growth and time and money constraints, it has become increasingly difficult to adequately review and assimilate relevant literature on any one subject. To address this problem, the Environmental Protection Agency's Health Effects Research Laboratory (HERL), using resources from EMIC and ETIC, has provided for the extraction of specific data to generate Graphical Activity Profiles (GAPs).

GAPs provide a way to demonstrate the genetic or developmental activity of a compound, both qualitatively and quantitatively. Each profile is plotted from data available in the open literature and keyed to a three-letter code indicating the test system, e.g., animal, activation, time frame, and the end point examined. The lowest effective dose (LED) or highest ineffective dose (HID) is obtained from references reviewed for each

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code and is translated into the logarithmic dose unit [$LDU_{(ij)}$] for a given test system (i) and chemical (j) as represented by the expressions:

$LDU_{(ij)} = -\log_{10}$ (dose) for HID ,

$LDU_{(ij)} = 5-\log_{10}$ (dose) for LED .

Using these data, a pictogram of the agent's activity, including its quantitative and qualitative parameters, is generated. The activity can be displayed phylogenetically or according to biological end point.

These extractions and profiles can reduce the effort necessary to determine the potential risk of an agent. Profile information can also be used to compare results across multiple assay systems; to compare the activity of different agents, including calculation of relative potencies; to aid in structure-activity studies; and to identify research needs. GAPs are novel and useful tools for characterizing an agent's biological activity at a glance.

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Human Genome Management Information System

Betty K. Mansfield, Anne E. Adamson, Roswitha T. Haas, Donald G. Kilgore, Michael D. Mayes, Elizabeth T. Owens, Judy M. Wyrick, and Laura N. Yust, Oak Ridge National Laboratory

The Human Genome Management Information System (HGMIS), cosponsored by the U.S. Department of Energy (DOE) and the National Institutes of Health (NIH), has roles in the International Human Genome Project to:

(1) assist agencies that administer genome research in communicating issues relevant to the human genome project to contractors and grantees and to the public and

(2) provide a forum for exchange of information among individuals involved in genome research.

To fulfill these communications goals, HGMIS is producing a bimonthly newsletter, DOE Human Genome Program reports, an information database, and technical reports. HGMIS updates and maintains the mailing list database compiled for the human genome programs of both DOE and NIH. Additionally, HGMIS acts to orient and refer those persons seeking assistance to sources that can provide appropriate information. These documents/services are available to all persons upon request and provide both the interested scientist and lay person with information in this rapidly moving, multidisciplinary project.

- The newsletter, *Human Genome News* (ISSN # 1050-6101), provides readers with technical and general interest articles, meeting reports, news items, funding announcements, and meeting and training calendars. Working in collaboration with the international Human Genome Organization, HGMIS also reports international genome project news.
- The status of the DOE Human Genome Program is described in the *Human Genome 1991-92 Program Report*, which includes research highlights, narratives on major DOE research efforts, abstracts of research in progress, and figures and captions provided by investigators.
- The information database is being developed as a text management and user conferencing mechanism and contains text from program reports and newsletters as well as bibliographic data from both the scientific and popular literature.

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Chemical Unit Record Estimates Database

David J. Reisman and Christopher T. DeRosa, U.S. Environmental Protection Agency and Mary W. Francis, Ida C. Miller, Robert S. Stafford, Andrew A. Francis, Cheryl B. Bast, and Po-Yung Lu, Oak Ridge National Laboratory*

The Chemical Unit Record Estimates (CURE) database, developed by the U.S. Environmental Protection Agency (EPA) in cooperation with the General Toxicology Program of Oak Ridge National Laboratory (ORNL), organizes information related to health risk assessment. In 1987, the Office of Health and Environmental Assessment (OHEA) of EPA began an extensive project to provide data to researchers in a variety of output formats and to computerize the quantitative health risk assessment documentation in a format that would support information transfer. The Chemical Unit Record Estimate (CURE) database is an on-line interactive database that provides (1) a compilation of numeric health risk estimates and accompanying experimental data, including data on target organs and on critical and secondary effects at varying doses; (2) side-by-side comparison of various related risk data; (3) an historical collection of health risk estimates generated by OHEA over the past 10 years on approximately 1400 chemicals; and (4) the ability to provide numeric output data sets of previously compiled research for testing current and future health risk assessment predictive models. The software and database design allow for rapid updating and for the addition of new data fields to both old and new records. The CURE database presently resides on an IBM mainframe computer at ORNL. PC versions of CURE have been developed and offer alternatives to on-line interaction with the mainframe computer. Both versions of the CURE database will be available for demonstration.

*Now affiliated with Agency for Toxic Substances and Disease Registry.

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Environmental Mutagen Information Center File

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The Environmental Mutagen Information Center (EMIC) was created in 1969, a time when geneticists were becoming more concerned about the possible genetic effects of environmental agents. These concerned geneticists founded the Environmental Mutagen Society (EMS), and its first charge was the formation of a register of chemicals tested for mutagenicity in different systems [*Mutation Research* **8** (1969), 671]. This registry was the beginning of EMIC.

Today the EMIC file contains over 72,000 indexed publications reporting on more than 22,000 chemical, physical, and biological agents. The file has developed during the last 21 years to respond to the needs of genetic toxicologists, regulators, students, and educators. In addition to test objects used and agents tested, indexing has evolved to include assay systems and end points, cells cultured, types of cells treated and observed (somatic or germ), and agents used as controls and inducers.

The U. S. Environmental Protection Agency (EPA), with the help of the staff at EMIC, used the file as a basis for the GENE-TOX Program, which continues to evaluate chemicals tested in validated assay systems. EPA's Health Effects Research Laboratory in North Carolina has used EMIC as a source of data and expertise for the generation of Graphic Activity Profiles.

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EMIC is funded by EPA and the National Toxicology Program of the National Institute of Environmental Health Sciences through the National Library of Medicine. The file is available on the NLM's TOXNET and TOXLINE systems.

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Environmental Teratology Information Center File

Geraldine S. Danford, Shigeko Y. Uppuluri, and Florence M. Holland, Oak Ridge National Laboratory

The thalidomide incident and the awareness of environmental effects on human health in the 1960s resulted in a great increase in the volume of scientific papers dealing with teratology. The Environmental Teratology Information Center (ETIC) was established in 1975 to collect, index, and computerize systematically the literature in this research area. This work continued actively until the end of 1989. The ETIC file that covers the literature published during the 1950-1989 era may be accessed via the National Library of Medicine's TOXLINE and TOXNET systems. The ETIC file is still maintained and is used to support several ongoing projects at the Laboratory. There are now more than 50,000 entries from over 3700 sources in the ETIC file. Copies of complete original documents are available for each entry. Each ETIC entry represents a publication from the open literature. For a paper to be accepted for the ETIC database, it must discuss the testing and evaluation of the developmental toxicity or reproductive effects of an agent whether the results are positive, negative, or inconclusive. Agents may be chemical, biological, or physical, and may also include dietary deficiencies and disease conditions in the mother. ETIC focuses mainly on the administration of an agent to a pregnant animal and the examination of the offspring at or near birth for either structural or functional anomalies. Also contained in the ETIC file are reports of epidemiological studies and clinical cases in humans, testing methods, in vitro studies, proposed rapid screening methods, placental transfer studies, reproductive and/or fertility studies, and studies of the reproductive effect of agents administered before pregnancy.

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Gene-Tox Agent Registry File

Roswitha T. Haas, Oak Ridge National Laboratory, and Angela E. Auletta, U.S. Environmental Protection Agency

The Gene-Tox Agent Registry File is the primary data compilation of the U.S. Environmental Protection Agency's Genetic Toxicology Program, a multiphase effort to evaluate the effects of chemical agents in selected short-term bioassays for genotoxic activity. The file contains results for over 4600 chemicals, extracted from the literature published from 1968 to the present. Panels of scientists who are authorities on particular test systems read publications in their respective fields and made decisions on the effect of test agents. The file resides in the ORLOOK data management system, run by an IBM 3033 computer.

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The biological information in the file is qualitative and is listed as positive, negative, or non-definitive results for 73 bioassays. These 73 tests can be grouped by gene mutation, chromosome aberration, other genotoxic effects, and in vitro cell transformation assays. The chemical information is contained in two main classification schemes, one by functional groups and one by ring systems.

The file is used to determine the sensitivity of each bioassay in response to specific classes of chemicals and to devise specialized batteries of assays that detect the various types of genetic damage induced by specific classes of chemicals.

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Genetic Toxicology Chemical Structure File

Roswitha T. Haas, Mary Ann C. Davidson, and K. S. Rao, Oak Ridge National Laboratory

The Genetic Toxicology Chemical Structure File is part of the U.S. Environmental Protection Agency's Genetic Toxicology Program, a multiphase effort to evaluate the effect of chemical agents in selected short-term bioassays for genotoxic activity. The database contains information on over 4600 chemicals.

The structure file uses the ChemBase database management software for personal computers from Molecular Design Limited to store chemical structure diagrams in addition to conventional database fields such as Chemical Abstracts Service Registry numbers and names. For structure entry, the diagrams are drawn with a mouse. The structure field can be searched for the occurrence of structure fragments.

The structure file is used to identify groups of chemicals with common substructures, to find structure-activity relationships, to visualize structures, and to print structure diagrams and tables of structure diagrams for viewgraphs, slides, and publications.

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Environmental Restoration and Waste Management Data Bases

Park T. Owen, Linda F. Goins, and Nancy P. Knox, Oak Ridge National Laboratory

In 1979 the U.S. Department of Energy (DOE) established the Remedial Action Program Information Center (RAPIC) at Oak Ridge National Laboratory to provide technical information support to the U.S. Department of Energy's Remedial Action Programs, which comprise Formerly Utilized Sites Remedial Action Program (FUSRAP), Surplus Facilities Management Program (SFMP), and Uranium Mill Tailings Remedial Action Program (UMTRA). In addition to these ongoing programs, RAPIC also serves the other groups within the DOE Office of Environmental Restoration. Specific information activities that RAPIC performs to support the DOE programs include maintaining a computerized bibliographic database containing approximately 7000 annotated references; publishing an annual bibliography, *Nuclear Facility Decom-*

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missioning and Site Remedial Actions, A Selected Bibliography, ORNL/EIS-154; maintaining a document repository and providing copies of requested publications; and performing manual and computerized searches of the technical literature. The most important RAPIC function is serving as a focal point for remedial action information. With these extensive resources at its command, RAPIC is in a unique position to provide a comprehensive information base to the remedial action and environmental restoration community.

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Development of Applicable or Relevant and Appropriate Requirements (ARARs) for Remediation of Hazardous Waste Sites Under Superfund

Elizabeth L. Etnier, Patricia S. Hovatter, Sylvia S. Talmage, Rose S. Weaver, Linda M. Houlberg, Robert H. Ross, Oak Ridge National Laboratory, and Robert Muhly, U.S. Army, Toxic and Hazardous Agency*

The U.S. Environmental Protection Agency (EPA) has established the National Priorities List (NPL) to prioritize for the states and the public those waste sites in the United States that have known or threatened releases of hazardous pollutants or contaminants into the environment. The U.S. Department of Energy (DOE) Oak Ridge Reservation (ORR) was listed on the final NPL on November 21, 1989. The U.S. Army currently has 17 installations listed on the final NPL. As a result of this listing, remediation at these sites must proceed according to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980, the Superfund Amendments and Reauthorization Act (SARA) of 1986, and the National Contingency Plan (NCP).

SARA specifies that remedial actions for cleanup of hazardous substances comply with applicable or relevant and appropriate requirements (ARARs) or standards under federal and state environmental laws. Inherent in the interpretation of ARARs is the assumption that protection of human health and the environment is ensured. ARAR reports are currently being developed for the DOE ORR and the U.S. Army. These reports highlight the chemical-, location-, and action-specific issues of concern for each waste site.

*Current organization Army Environmental Center

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Selection of Indicator Chemicals at Hazardous Waste Sites

Patricia S. Hovatter and Robert E. Gibson, Oak Ridge National Laboratory, and Robert Muhly, U. S. Army*

According to the Environmental Protection Agency (EPA) methodology outlined in the 1989 *Risk Assessment Guidance for Superfund* the first step in the baseline risk assessment at Superfund sites is data collection and evaluation, which involves the selection of indicator chemicals. This procedure identifies the chemicals that pose the greatest potential public health risk at a site and is based on site monitoring data, chemical toxicity information, and environmental persistence and mobility of the chemicals. A computer program (CASIC), using Lotus 1-2-3 spreadsheets, was developed to automate the routine features of the procedure. Initially, a concentration-toxicity screening method is used to obtain a ranking of the relative risk for each detected chemical in a specific environmental medium. A risk factor for each chemical is calculated as the maximum detected concentration in the particular medium times a toxicity factor, which is the reference dose for noncarcinogens or the carcinogen potency factor for carcinogens. The most current toxicity factors are obtained from either the EPA Integrated Risk Information System (IRIS) database or the quarterly EPA Health Effects Assessment Summary Tables. The top-scoring chemicals in the screening procedure, along with any detected chemicals for which toxicity factors are currently unavailable, are subsequently analyzed to establish a potential list of indicators for final selection. Final selection of indicators is then based on evidence of human carcinogenicity, frequency of occurrence in environmental media, exceedance of acceptable intake values, exceedance of background levels, and the migration potential and environmental persistence of the chemicals.

*Current organization Army Environmental Center

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Less-Than-Lifetime Risk Assessment: Estimation of No-Effect Levels for Nonlethal Toxic End Points by Analogy to Acute Toxicity

Cheryl B. Bast and Robert E. Gibson, Oak Ridge National Laboratory, and Christopher H. Cubbison and Christopher T. DeRosa, U.S. Environmental Protection Agency*

Data necessary for establishing human no-observed-adverse-effect levels (NOAELs) are not available for many chemicals, whereas acute toxicity data are often readily available. If the existence of a relationship between acute toxicity data and NOAELs were to be established for those chemicals for which both types of data exist, it would then be possible to estimate a NOAEL for some chemicals for which only the acute toxicity data exist. Over 1100 chemicals from the Chemical Unit Record Estimates (CURE) database of the U.S. Environmental Protection Agency were classified according to the 30- or 69-class scheme used for the Gene-Tox Program. No-effect levels and acute toxicity data (from the Registry of Toxic

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Effects of Chemical Substances) were incorporated into a less-than-lifetime database, and the log(LD_{50}/NOAEL) was determined. The percentage of chemicals included by a given ratio was then calculated for various chemical classes for oral exposure in rats. Data suggest that both the LD_{50}s and NOAELs are normally and independently distributed. The upper limit for a NOAEL can be estimated by the use of a factor of 10,000 to 100,000, but the probability is high that the no-effect level will be underestimated by several orders of magnitude.

*Now affiliated with Agency for Toxic Substances and Disease Registry

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PATS: Packaging and Transportation Safety Program Data Base

Ruth M. Gove, Andrea A. Richmond, Miriam J. Welch, and Richard R. Rawl,
Oak Ridge National Laboratory

The Department of Energy Assistant Secretary for Environment, Safety, and Health is charged under DOE Order 5480.3 with safety overview responsibilities for the packaging and transportation of hazardous materials, substances, and wastes at all DOE facilities. The Packaging and Transportation Safety (PATS) Program is the means by which these responsibilities are addressed. Oak Ridge National Laboratory (ORNL) serves as the integrator for the PATS Program.

The PATS database was initiated in 1989 to organize information related to DOE packaging and transportation safety activities. It contains specific site information regarding DOE facilities, appraisal visit schedules and reports, appraiser names, training, and expertise.

The database is maintained on a PC using dBase III and Clipper software. The user can select reports based on such things as hazardous class, site/facility names, and appraiser name.

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Toxicology Guide for Installation Restoration Program Application

Robert A. Young, Po-Yung Lu, Mary W. Francis, and Robert H. Ross,
Oak Ridge National Laboratory, and
G. W. Jepson and J. W. Fisher, Wright-Patterson Air Force Base, U.S. Air Force

Under the Installation Restoration Program, the U.S. Air Force is required to provide comprehensive chemical profiles of toxic or hazardous chemicals commonly found at Air Force installations. Four volumes (2500 pages) of peer-reviewed reports covering 70 chemicals will be used by all Air Force

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installations (both domestic and overseas), nearby communities, and state and local governments. This Toxicology Guide provides two categories of information: (1) concise summaries and (2) in-depth evaluations. The summaries include substance identification, air w/v conversion factors, reactivity and physico-chemical data, pathways of exposure, persistence in soil/groundwater systems, health hazard data, handling precautions, environmental and occupational standards and criteria, and regulatory status (federal, state, and European Economic Community directives). The evaluations include environmental fate, human health effects (carcinogenicity, teratogenicity, genotoxicity, short- and long-term toxicity), and sampling and analysis information. A fifth volume covering six metals of concern is in preparation.

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Hypertext System Demonstration: Information on the Symposium and BEIA

Gloria M. Caton and Suzanne E. Joy, Oak Ridge National Laboratory

A hypertext demonstration provides information on the symposium on Access and Use of Information Resources in Assessing Health Risks from Chemical Exposure, the Biomedical and Environmental Information Analysis (BEIA) Section, and local area attractions.

The mission of BEIA and the expertise and capabilities of BEIA staff members are summarized. Information is given on the following groups and their projects: the Human Genome and Toxicology Group, the Chemical Hazard Evaluation and Communication Group, the Environmental Regulations and Remediation Group, and the Information Management Technology area.

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Activities of the Federal-State Toxicology and Regulatory Alliance Committee

Robert Cantilli, U.S. Environmental Protection Agency

The Federal-State Toxicology and Regulatory Alliance Committee (FSTRAC) was formed in 1985 to facilitate cooperation between federal and state regulators and risk assessors on drinking water issues. FSTRAC is composed of representatives from state health and environmental agencies, the U.S. Environmental Protection Agency (EPA), Office of Drinking Water, and EPA regional programs. FSTRAC brings together professionals with many different areas of expertise to develop well-rounded, integrated approaches to risk assessment and standard-setting issues. In a broad sense, EPA sponsors FSTRAC to foster cooperation among states, and between states and EPA; provide a setting for informal and formal discussions of common problems; improve consistency between federal and state approaches to setting drinking water standards or guidance; obtain feedback on federal or state guidance and standards; and discuss factors influencing state risk assessment and regulatory programs. Specific activities and products of FSTRAC include workshops on risk assessment methodologies commonly used by EPA and states; panel

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discussions between FSTRAC members on practical solutions to risk assessment problems; guidance documents on chemical mixtures in drinking water; a summary of state and federal drinking water guidelines and standards; an electronic seminar series in which states and EPA share information on recent risk assessment developments through teleconferencing; a guidance document on assessing noningestion exposures to drinking water contaminants; and a risk communication bibliography and a number of nation-wide surveys on the occurrence, regulations, and guidance for drinking water contaminants.

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The Rodent Dominant Lethal Assay

Bradford L. Whitfield, Oak Ridge National Laboratory

The rodent dominant lethal assay is one of the short-term genotoxicity tests selected by the U.S. Environmental Protection Agency for inclusion in the Gene-Tox Program (other posters at this meeting describe the Gene-Tox Program). This poster provides details of the dominant lethal assay and uses the Gene-Tox evaluation of this assay as an example of the ability of the Biomedical and Environmental Information Analysis (BEIA) Section Human Genome and Toxicology (HGT) Group to provide scientific and information support to other groups and government agencies.

The Environmental Mutagen Information Center (EMIC), one component of HGT, has for 21 years been identifying, collecting, and extracting the technical information from the published literature in genetic toxicology. This extensive computerized database and the expertise of the EMIC staff are instrumental in the continuing success of the Gene-Tox Program.

Published literature on the dominant lethal assay had already been identified, and copies of the publications were available at EMIC; thus it was quick and easy to obtain a subset of the literature dealing with this assay. After an initial screening of the literature by the EMIC staff, copies of the pertinent papers were distributed to the Gene-Tox panel of experts for critical evaluation. The EMIC staff member assigned to the panel contributed both as a scientist and as an information specialist. The final report of the panel was published in open literature, and the results were entered into the Gene-Tox database at ORNL. Newly published data are evaluated and added to the database on a continuing basis.

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In Vivo Micronucleus Assay in Mammalian Bone Marrow and Peripheral Blood

Kathleen H. Mavournin, Oak Ridge National Laboratory;
David H. Blakey, Department of National Health and Welfare, Canada;
Michael C. Cimino, U.S. Environmental Protection Agency;
Michael F. Salamone, Ontario Ministry of the Environment, Canada; and
John A. Heddle, York University, Canada

The protocol recommended for the micronucleus assay in mammalian bone marrow has been revised and simplified. The number of sample times has been reduced to one or two, depending upon the dosing protocol. The minimum number of cells to be scored per treatment group has been increased to 20,000 to increase the ability of the assay to detect a doubling of the control micronucleus frequency. Use of both male and female animals is recommended. Scoring of micronuclei in polychromatic erythrocytes of peripheral blood is included as a variation of the bone marrow assay. Published data on chemicals tested by the micronucleus assay have been reviewed and are summarized.

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Inhalation Reference Dose Methodology: Development, Dosimetric Adjustments, and Human Equivalent Concentrations

Chon R. Shoaf and Annie M. Jarabek, U.S. Environmental Protection Agency

Information resources are the critical basis for initiating inhalation reference dose (RfD_i) development. The information retrieval method includes a complete and current literature search, information abstraction, database construction, and compilation of the concentration-response data. When such an information retrieval method is coupled with a physiologically-based dosimetry model, human equivalent concentrations integral to the RfD_i development process can be derived. Critical studies chosen from the literature searches provide the necessary information on health effects to which extrapolation methods for high-to-low dose, animal-to-human extrapolations, and normal-to-susceptible subpopulations are applied. The concentration response database should yield the no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL). Other necessary data include characteristics of the aerosol or gas (mass medial aerodynamic diameter, particle distribution, temperature, pressure) and the appropriate respiratory tract region (extrathoracic, tracheobronchial, pulmonary, or total) or other organ manifesting the toxic effect. Data bases of animal and human physiological, anatomical, and metabolic parameters will continue to play an important role in reducing uncertainty in the RfD_i by providing information for mathematical models of empirical data and physiologically based pharmacokinetic models to support dosimetric adjustments and more accurate risk estimates. (This abstract does not necessarily reflect EPA policy.)

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Animal Testing Alternatives: A Selected Annotated Bibliography

Robert S. Stafford and Po-Yung Lu, Oak Ridge National Laboratory, and George J. Cosmides, National Library of Medicine

The scientific community is concerned about animal welfare and is also sensitive to public concerns regarding how and why animals are used in biomedical research and toxicological testing. Although it is unlikely that alternatives to animal methods or in vitro methods will ever satisfy all the requirements of research and testing, alternatives to the use of intact animals (vertebrates) are being developed. Research on methodology is aimed at refinement of procedures to reduce pain and discomfort, reduction in the number of experimental animals necessary for scientifically valid results, and replacement of intact vertebrates when scientifically acceptable alternatives can be verified and validated.

The purpose of this series of quarterly bibliographies is to provide periodic literature surveys in a format that facilitates easy scanning. Citations with annotations relating to the method are organized under categories such as cell culture or a specific target organ. The bibliographies feature selected citations that deal in some predominant way with methods, assays, tests, or procedures that may be useful alternatives to intact vertebrates. The citations are selected and compiled after monthly on-line searching of appropriate bibliographic databases on the computer system of the National Library of Medicine. These bibliographies are available, free of charge, to interested organizations or individuals.

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Superfund Technology Support Center for Health Risk Assessment

Pei-Fung Hurst, W. Bruce Peirano, and Christopher T. DeRosa, U.S. Environmental Protection Agency*

In December 1989, the Office of Health and Environmental Assessment (OHEA) was designated, in a memorandum of understanding between the Office of Research and Development (ORD) and the Office of Solid Waste and Emergency Response (OSWER), as the location for the Superfund Technical Support Center (TSC) for human health risk issues. The Environmental Criteria and Assessment Office (ECAO) will function as the focal point to coordinate OHEA- or agency-wide assistance in this area. A hot line has been established [FTS 684-7300 or (513) 569-7300] to facilitate the communication between the TSC and the Superfund risk assessors.

OHEA has a long history of providing support to different regulatory programs, has experience with chemical review and toxicity evaluation, and has an excellent working relationship with other ORD labs and program offices. These factors place OHEA in a unique position for providing assistance in health risk assessment. This assistance will be conducted in conjunction with the Toxics Integration Branch (TIB) of the Office of Emergency and Remedial Response (OERR) in order that future research and Superfund

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program issues may be identified and to ensure consistent responses to policy questions and specific situations with broad application. In order to encourage interaction and information exchange, OHEA and TIB/OERR will convene a risk assessment round table with the regions. Regional representatives are encouraged to participate in the monthly Risk Assessment Teleconference for Superfund (RATS) with TIB and OHEA to ensure that consistent approaches are applied across all National Priority List (NPL) sites and to identify policy issues.

The specific function of the health risk TSC is to provide a rapid response to specific questions by telephone and written follow-up, when appropriate, to regional toxics integration coordinators (RTICs), remedial project managers (RPMs), on-scene coordinators (OSCs) and regional Superfund staff relating to chemical-specific health information. Contractors may also contact the TSC with site-specific Superfund questions, but may be required to route the question through their RTIC, RPM, etc. In any event, these people will be notified of the question and the response.

Clarification and interpretation of the Risk Assessment Guidance for Superfund (RAGS) will be coordinated with the TIB. OHEA will also consult with other offices and programs, when necessary, to respond to multifaceted questions such as route-to-route extrapolation, dermal risk parameters, and less-than-lifetime exposure. Coordinated responses will also be provided on health-based triggers and cleanup levels and justification for surrogate cleanup levels based on default assumptions.

Utilization of the TSC is expected to be extensive. The TSC is already responding to between six and ten calls per day prior to any extensive publicity. This TSC has been designed for maximum flexibility in order to respond to a wide variety of assistance requests. With the help of the TIB, the Regional Forum and other agency offices, the TSC should prove extremely valuable to the entire Superfund program by providing timely, consistent, state-of-the-science answers to complex questions.

*Now affiliated with Agency for Toxic Substances and Disease Registry.

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Chemical Hazard Assessment

Robert H. Ross, Cheryl L. Bast, Mary L. Daugherty, Kowetha A. Davidson, Rosmarie Faust, Andrew A. Francis, Patricia S. Hovatter, Dennis M. Opresko, Sylvia S. Talmage and Robert A. Young, Oak Ridge National Laboratory, and Christopher T. DeRosa, Harlal Choudhury, V. J. Cogliano, Christopher H. Cubbison, and Bennett G. Smith, U.S. Environmental Protection Agency*

The assessment of the health and environmental hazards posed by the environmental release of chemicals is an information-intensive process. An assessment can be qualitative, quantitative, or a combination of both, the latter being most common. Qualitative assessments convey the risk of exposure to a chemical to the extent that the potential hazards are clearly identified, but exposure levels of concern are not derived. On the other hand, quantitative hazard assessments are processes by which levels of concern are derived. The methodology for conducting hazard assessments involve computer-aided scans of the literature, selection of all relevant human and animal studies that make up the database, selection of key studies that identify and characterize the critical effect and dose-response relationships, and use of dose-response data points in specific equations or computer models to calculate the specific risk values. An example of a qualitative hazard assessment is the carcinogen classification schemes used by the Environmental Protection

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Agency and the International Agency for Research on Cancer. Examples of quantitative assessments include reference doses, slope factors, reportable quantities, and water quality criteria. Because each of these quantitative risk assessments can be derived on the basis of a single well-conducted study, access to all available information is essential to ensure that all relevant studies have been considered.

*Now affiliated with Agency for Toxic Substances and Disease Registry

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Mutagenicity Testing Guidelines for the U.S. EPA Office of Toxic Substances (OTS)

Michael C. Cimino and Angela E. Auletta, U.S. Environmental Protection Agency

The U. S. Environmental Protection Agency (EPA) Office of Toxic Substance presently has 22 mutagenicity test guidelines, either existing, proposed or in draft. 20 have been published in the *Federal Register* (*FR*), and 19 appear in the *Code of Federal Regulations* (CFR). Eleven guidelines are widely used by OTS. The Ames guideline is considered current state-of-the-art and it is not scheduled for update. The in vitro gene mutation test is also widely-used; the L5178Y cell line is being split out as a separate assay, and the CHO and AS52 cell lines are also likely to be split out. The Drosophila sex-linked recessive lethal (SRL) test, used in Sect. 4 test rules, will likely be replaced with alternative test(s), and is not scheduled for up-date. The visible SLT, the 3rd-tier test rule standard, is considered state-of-art; minor modifications have been proposed in the *FR*. The biochemical SLT has been proposed as an alternative to the visible test; a final guideline should be published by January of 1990. The in vitro chromosome aberration test is widely-used; these are currently undergoing revision. The in vivo spermatogonial chromosome aberration test is new for OTS. The rodent dominant lethal is widely-used, and will be revised soon. The heritable translocation test is a 3rd-tier standard in test rules, but is considered state-of-art and is not scheduled for update. Although intended as recommendations for conducting the subject assay for submission of data to EPA, OTS guidelines, along with relevant modifications, become test standards when cited in a test rule.

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Material Safety Data Sheets for Hazard Communication

Sibyll M. Hubner, Betty W. Kline, Po-Yung Lu, and Linda B. Pierce, Oak Ridge National Laboratory, and James R. Crawl, Environmental Health Center, Norfolk, U.S. Navy

The Occupational Safety and Health Administration Hazard Communication Standard 29 CFR 1900.1200 requires manufacturers, distributors, users, and importers to communicate information to employees on all hazardous chemicals used in the workplace in the form of Material Safety Data Sheets (MSDS). Also, Superfund Amendment Reauthorization Act, Title III, Sections 311 and 312, cites

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MSDS as a means of fulfilling community right-to-know reporting requirements. The Oak Ridge National Laboratory (ORNL) uses the Hazardous Substances Data Bank, the U.S. Environmental Protection Agency Gene-Tox Data Base, other pertinent databases, reference books, and manufacturers' information to prepare MSDS. Selected MSDS are peer-reviewed to ensure that they accurately reflect what is known about the chemical or trade name products. Currently, information on 2661 pure chemicals and 5136 trade name products is available through a menu-driven retrieval system developed using INQUIRE on an IBM mainframe computer, which allows on-site or off-site access. The MSDS at ORNL are kept current by updating such selected data elements as threshold limit value, toxicity, and cancer rating. In addition, a total of 2000 MSDS have been prepared for the U.S. Navy and Army to be incorporated into the Department of Defense Hazardous Materials Information System. Information obtained primarily from manufacturers' MSDS has been enhanced to update threshold limit values, toxicity, and cancer ratings.

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DART and Other Information Resources in Developmental and Reproductive Toxicology

Carole A. Kimmel, Environmental Protection Agency, Stacey J. Arnesen and Henry M. Kissman, National Library of Medicine, and Bernard A. Schwetz, National Institute of Environmental Health Sciences

The DART (Developmental and Reproductive Toxicology) database is a new bibliographic database intended to provide a comprehensive collection of the available literature in developmental and reproductive toxicology. DART is a continuation and expansion of the ETIC (Environmental Teratology Information Center) database, which was established originally by the National Institute of Environmental Health Sciences (NIEHS) and produced by Oak Ridge National Laboratory (ORNL). Currently, DART contains references to literature primarily in developmental toxicology dating from 1989; ETIC covers literature of similar scope from 1950 to 1988. Both DART and ETIC (as ETICBACK) are available on line via the National Library of Medicine (NLM) TOXNET (Toxicology Data Network) system. DART is currently funded by NIEHS, the Environmental Protection Agency (EPA), and the Agency for Toxic Substances and Disease Registry (ATSDR), through agreements with NLM, which provides support and oversees the maintenance of the database. The scope of DART will be expanded soon to include other areas of reproductive and developmental toxicology that have not been covered previously; at least 3600 references will be added each year, both from NLM's MEDLINE database (approx. 60%) and from non-MEDLINE sources, such as books, meeting abstracts, technical reports, and journals not indexed for MEDLINE. These records will contain abstracts, MeSH (Medical Subject Headings) indexing, and complete chemical indexing. A summary of other information resources available in developmental and reproductive toxicology (e.g., REPROTOX, Shepard's Catalog, TERIS, etc.) also will be provided.

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The Ames/Salmonella Microsome Assay for Genotoxicity

Mary M. Brown and Elizabeth S. Von Halle, Oak Ridge National Laboratory, and Angela E. Auletta, U.S. Environmental Protection Agency

The number of chemicals for which published data in the Salmonella assay (SAL) have been evaluated and entered into the GENE-TOX EPA database is 2469. Of these, 666 are reported to be SAL+ (positive), 416 SAL+-* (positive with metabolic activation), and 18 SAL+ (positive without metabolic activation and negative with metabolic activation). Collectively, 1100 chemicals were positive in the SAL assay, 880 negative, and 489 were inconclusive. Comparative results between chemicals tested in SAL and a variety of other test are available in Gene-Tox database. For example, of the 2469 compounds tested in SAL, 326 results for animal carcinogenicity (CCG), 108 for mutations in Chinese hamster lung cells (V79), 122 for sex-linked recessive lethals in Drosophila (SRL), 156 for cell transformation in mammalian cell systems (CT). The number of noncarcinogens reported in the Salmonella database increased from 14 in the original Gene-Tox review to 58 in the present update. These data are used to compare sensitivity, specificity, concordance, and predictivity in the different test systems with carcinogenicity in animals. Comparisons are also made of test results of genotoxicity in Salmonella with genotoxicity in eucaryotes.

When the limited positive and negative results for animal carcinogenicity (CCG+L and CCG-L) are removed from the calculations, the sensitivity (78.36 to 82.93%) and concordance (76.07 to 80.00%) of the Salmonella test increased without a significant decrease in specificity (65.52 to 65.00%). Elimination of these data from the comparisons results in values for sensitivity, concordance, and specificity values similar to those obtained with pre-1979 data when only 14 noncarcinogens were available for comparison.

Combining genotoxicity data obtained from the V79 and SRL test systems with the Salmonella data does not improve the correlation with carcinogenicity. The cell transformation data do not correlate as well as the Salmonella data with carcinogenicity but do have a higher predictivity for noncarcinogens, although this value is only in the 50% range.

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Proposed Changes to the Toxic Substances Control Act (TSCA) Tier Testing Scheme for Mutagenicity

Angela E. Auletta and Michael C. Cimino, U.S. Environmental Protection Agency

Under the Toxic Substances Control Act (TSCA) EPA may require testing in the areas of "carcinogenesis, mutagenesis, . . . and unreasonable risk . . . to health or the environment." Chemicals are tested for gene and chromosomal mutation using tier schemes designed to detect intrinsic mutagenicity, determine if the chemical reaches the gonad and interacts with germ cell DNA, and detect the induction of heritable mutations in mammals. Positive responses in key tests also serve as triggers to a bioassay. The

33 *continued* . . . . . .

gene mutation scheme begins with an Ames assay. An in vitro test for gene mutation is performed if the Ames assay is negative. A positive response in either test triggers a Drosophila sex-linked recessive lethal (SRL) test; a positive SRL response triggers a visible or biochemical-specific locus test. The cytogenetics scheme begins with an in vitro cytogenetics test. An in vivo cytogenetics test is performed if the in vitro assay is negative. A positive response in either test leads to a dominant lethal test; a positive dominant lethal response leads to a rodent heritable translocation test. A bioassay is triggered if both the Ames *and* the SRL tests are positive *or* if the in vitro gene mutation test *or* the in vitro *or* in vivo cytogenetics tests are positive. It is proposed to combine the first tier of both schemes, to replace the SRL test with a test or tests for direct effects on gonadal DNA such as the induction of UDS or SCE in testicular tissue, to eliminate the single test trigger to a bioassay, and to have any combination of tests leading to a bioassay include a positive response in an in vivo test for chromosomal damage.

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Radiological Site Characterization Surveys and Data Analyses

Mary S. Uziel, Lois M. Floyd, and Judy W. Crutcher, Oak Ridge National Laboratory

The Measurement Applications and Development (MAD) Task Group of the Biomedical and Environmental Information Analysis Section, Oak Ridge National Laboratory, has the primary responsibility of writing technical reports based on radiological characterization surveys conducted by the Environmental Measurements and Applications Section. At the request of the U.S. Department of Energy (DOE), these investigative surveys are performed to determine whether a site is currently contaminated with radioactive residues derived from activities related to past projects of DOE or its predecessors.[1]

The surveys may encompass both indoor and outdoor examination of the site with direct and transferable measurements of alpha, beta, and gamma radiation levels; gamma scans; and collection of samples for radionuclide analyses.

Responsibilities of the MAD Task Group include participation in field surveys, analyses of site data, interpretation of results, digitization of survey site maps using CAD programs, development of computer programs to facilitate statistical analyses and graphical presentation of data, and recommendations for corrective actions where appropriate.

[1]DOE programs supporting the MAD Task Group include the Formerly Utilized Sites Remedial Action Program, the Remote Surplus Facilities Management Program, the Environmental Restoration Program, and the Environmental Regulations Program.

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Biomedical and Environmental Information Analysis Section Communication Resources: Printed and Electronic

Gloria M. Caton, Linda M. Houlberg, Marilyn E. Langston, and Judy M. Wyrick, Oak Ridge National Laboratory

Biomedical and Environmental Information Analysis (BEIA) personnel from different groups work together using technical, editing, and desktop publishing skills to produce scientific publications for a variety of projects and sponsors (internal and external). Technical information, research results, and research news are prepared and summarized in readily accessible formats for investigators, managers, and other interested parties. Examples of products from these integrated efforts include the following:

- **Newsletters**: *Radon Research Notes, Human Genome News, ESHNEWS,* and *Ceramic Technology for Advanced Heat Engines*;
- **Reports**: *Environmental Regulatory Update Table, Weekly Federal Register Digest, 1990 Inventory of Federal Hazardous Waste Activities at ORNL, Spill Prevention Control Countermeasures and Contingency Plans at ORNL,* and *ORNL Part B RCRA Permit Application for Remote-Handled Transuranic Concrete Cask Storage Facility*;
- **Books and Manuals**: Environmental Guidance Reference Books, and *VP-Expert: Rule-Based Expert System Development Tool for Personal Computers, Course Workbook*;
- **Regulatory Posters**: "Drinking Water Regulations" (with federal current/proposed drinking water criteria and the stricter state criteria); and
- **Hypertext Interactive Communication** (see demonstration describing symposium, BEIA, and local area attractions).

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Environmental Guidance Program: Reference Books and Regulatory Update Table

Cynthia G. Heckman, Linda M. Houlberg, Marilyn E. Langston, Patricia A. Nikbakht, Marti S. Salk, and Julia M. Stockstill, Oak Ridge National Laboratory

The mission of the Environmental Guidance Program, based at Department of Energy (DOE) headquarters in Washington, D.C., is to provide guidance to DOE in complying with various environmental laws and regulations. The Reference Books and Regulatory Update Table are two tools used to provide this guidance. The Reference Books provide information on major environmental statutes and their implementing regulations that appear to be most relevant to DOE activities. The 14 books are revised

36 *continued* . . . . . .

and distributed to DOE and contractor staff annually, although this may occur more often when required by major new developments in statute regulatory programs. The books are divided into four sections: Summary, Legislative History and Statutes, Implementing Regulations, and Updates. These reference books provide a convenient up-to-date source of information on each of the major environmental statutes. The Regulatory Update Table provides information on regulatory initiatives of interest to DOE operations and contractor staff with environmental management responsibilities. The table tracks regulatory developments and is updated each month with information from the *Federal Register* and other sources, including direct contact with regulatory agencies. Each table entry provides a chronological record of the rulemaking process for that initiative with an abstract and a projection of further action.

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Air Risk Information Support Center (Air RISC)—Technical Support to State and Local Agencies for Risk Assessment

Chon R. Shoaf and Daniel J. Guth, U.S. Environmental Protection Agency

The Air Risk Information Support Center (Air RISC) was initiated in early 1988 by the Environmental Protection Agency (EPA) Office of Health and Environmental Assessment and the Office of Air Quality Planning and Standards (OAQPS) as a technology transfer effort that would focus on providing information to state and local environmental agencies and to Environmental Protection Agency (EPA) regional offices in the areas of health, risk, and exposure assessment for toxic air pollutants. Provision of technical assistance to the state and local agencies is key to supporting their greater regulatory role as envisioned in the EPA's National Air Toxics Strategy announced in 1985. Technical information is fostered and disseminated by Air RISC's two primary activities—technical assistance and guidance projects on air toxic, health, and educational issues and staffing a "hot line" to provide immediate response to state and local inquiries. Technical assistance and guidance projects have included a wide variety of activities in risk assessment and risk communication, short-term assessments of hydrogen chloride, a glossary of terms related to risk assessment, a directory of information resources related to risk assessment, and training courses on risk assessment. In the 2 years since inception, the scientists at the Environmental Criteria and Assessment Office and OAQPS have responded to 1131 calls from state and local agencies. (This abstract does not necessarily reflect EPA policy.)

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Risk Assistant

John Schaum, Environmental Protection Agency and
John Young, Hampshire Research

Risk Assistant is a microcomputer-based software system being developed by the Environmental Protection Agency (EPA) in conjunction with Hampshire Research for the purpose of conducting risk assessments. It is designed to be applied to specific sites and chemicals. The user inputs the chemical concentration data at the point of exposure, and the system retrieves the relevant toxicological data, provides defaults for the various exposure parameters, and produces a report summarizing the results and important assumptions. The system uses a pull-down menu interface with on-screen help covering both operational and scientific information. It requires an IBM-XT equivalent or higher machine. The currently available version is a Beta-type, and a final release is scheduled for late 1990.

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Development and Application of Numeric Files Derived from Toxicologic Experimentation

Sidney Siegel, National Library of Medicine

Presented as a poster session will be rationale for the development and maintenance of information resources to be supportive of the efficient and cost-effective accomplishment of the assessment and management of risk.

Identified and outlined are issues relevant to the development, use, and acceptance of numeric files derived from published toxicologic experimentation.

Agenda

(All platform sessions for the symposium will be held in the Auditorium of the American Museum of Science & Energy. Poster sessions will be held in the Ballroom of the Garden Plaza Hotel. The American Museum of Science & Energy is located behind the Garden Plaza Hotel.)

Tuesday Evening, June 26, 1990

5:00-8:00 Registration (Garden Plaza Hotel)

Wilma J. Barnard, Conference Secretary, ORNL

Poster Setup

Entertainment

Moon Miller, Spring City, Tennessee

Wednesday Morning, June 27, 1990

7:00-8:00 Registration (Garden Plaza Hotel)

Wilma J. Barnard, Conference Secretary, ORNL

8:00 Symposium Introduction and Overview,
Po-Yung Lu, ORNL

(American Museum of Science & Energy)

Welcome *Stephen V. Kaye*, ORNL;
William H. Farland, EPA

8:10 Introduction, meeting overview, and purpose
Po-Yung Lu, ORNL

8:25-10:30 Chemicals, Health Effects, and Information Needs

Introduction *Po-Yung Lu*, ORNL, Chair

8:30 The problem of living in a world contaminated with chemicals

Robert L. Metcalf, University of Illinois

9:00 The environmental laws regulating chemicals

Jeffrey M. Gaba, Southern Methodist University

9:30 Information needs for risk assessment

Christopher T. DeRosa and *Rita S. Schoeny*, EPA

10:00 Information needs for risk management/communication

David A. Bennett, EPA

10:30-10:45 *Break*

10:45-12:15 Toxicology Information Resources, Challenges, and Needs

Introduction *John S. Wassom*, ORNL, Chair

10:45 Evolution of toxicology information systems

John S. Wassom, ORNL

11:15 Information and technology: a coexistence without limits, a beginning with no apparent ending...

David J. Reisman, EPA

11:45 The challenge of information access

Linda A. Travers, EPA

Wednesday Afternoon, June 27, 1990

12:15-1:30 *Lunch*

1:30-3:05 Application of Toxicology Information for Establishing Priorities for Chemical Testing, Hazard Ranking, and Assessment

Introduction *Babasaheb R. Sonawane*, EPA, Chair

1:35 Structure-activity relationships (SARs) to assess new chemicals under TSCA

Angela E. Auletta, EPA

2:05 Quantitative genetic activity graphical profiles for use in chemical evaluation

Michael D. Waters, EPA

2:35 Interagency Testing Committee chemical selection process

John D. Walker, ITC

3:05-3:20 *Break*

3:20-5:30 Guidelines Used to Assess Toxicological Haza[illegible]

Dorothy E. Patton, EPA, Chair

3:30 EPA's program for risk assessment guidelines: Overview

Dorothy E. Patton, EPA

4:00 Cancer classification issues

Jeanette Wiltse, EPA

4:30 Quantification issues

Michael L. Dourson, EPA

5:00 Exposure issues

Michael A. Callahan, EPA

Wednesday Evening, June 27, 1990

5:45-7:30 Poster Session/Demonstrations (Garden Plaza Ballroom)

Refreshments and Entertainment

Moon Miller, Spring City, Tennessee

Thursday Morning, June 28, 1990

8:00-10:00 Poster Session/Demonstrations (Garden Plaza Ballroom)

10:15-10:45 Rapporteur Summary *Sidney Siegel*, NLM

(American Museum of Science & Energy)

10:45-5:30 Information Applications

Introduction *Christopher T. DeRosa*, EPA, Chair

11:00-3:00 Panel discussion on how information resources are used by federal agencies in risk assessment applications

Penny Fenner-Crisp, EPA, Rapporteur

ATSDR *Deborah A. Barsotti*

DOD-US Army *William E. Legg*

DOE-ORO *Timothy W. Joseph*

EPA-Region III *Richard Brunker*

FDA *Angelo Turturro*

Thursday Afternoon, June 28, 1990

12:00-1:30 *Lunch*

NIOSH *Leslie T. Stayner*

NTP *James K. Selkirk*

USDA-FS *Dennis R. Hamel*

USDA-FSIS *Wesley A. Johnson*

2:20-3:00 Questions from audience

3:00-3:30 *Break*

3:30-5:30 Panel discussion on how information resources are used by state agencies in risk assessment applications

Stephen M. Dizio, California, Rapporteur

California *Stephen M. Dizio*

Connecticut *David R. Brown*

Illinois *Clark S. Olson*

Louisiana *Suzanne M. Gardner*

Massachusetts *Carol Rowan West*

	New Jersey *Gloria B. Post*
	Tennessee *Bonnie S. Bashor*
5:00-5:30	Questions from audience

Friday Morning, June 29, 1990

8:00-9:25	Information Files and Data Base for Evaluating Health Hazards From Chemical Agents (American Museum of Science & Energy)
	Introduction *Linda A. Travers*, EPA, Chair
8:05	Rapporteur summary of session on information applications
	Federal agency perspective: *Penny Fenner-Crisp*, EPA
	State agency perspective: *Stephen M. Dizio*, California
8:45	EPA data bases for risk assessment
	Linda Tuxen, EPA
9:05	ORNL data bases for health effects assessment
	Po-Yung Lu, ORNL
9:25-12:30	Information Resource Development/Integration/ Communication/ Transfer for Assessing Health Effects from Chemical Exposure
	Introduction *Robert H. Ross*, ORNL, Chair
9:30	Application of the Federal Technology Transfer Act to health risk assessment
	Larry Fradkin and *Christopher T. DeRosa*, EPA
10:00-10:10	*Break*
10:10-12:00	Panel discussion on information resources for assessing health effects from chemical exposure: Challenges, priorities, and future issues
	William H. Farland, EPA, Moderator
	Deborah A. Barsotti, ATSDR
	Penny Fenner-Crisp, EPA
	Chon R. Shoaf, EPA
11:00-11:15	*Break*
	Bonnie S. Bashor, Tennessee
	Robert O. Beauchamp, Jr., CITE
	Heinrich V. Malling, NIEHS
	Sidney Siegel, NLM
	Linda A. Travers, EPA

Friday Afternoon, June 29, 1990

12:00-12:30	Questions from audience
12:30-1:00	Concluding Remarks: Where Do We Go From Here?
	William H. Farland, EPA
1:00	Adjournment
2:30	ORNL Overview (Optional)
	Truman D. Anderson, ORNL

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