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HEALTH EFFECTS OF RISK-ASSESSMENT CATEGORIES

C.F. Kramer, K. Rybicka, A. Knutson, and S.C. Morris

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A.A. Moghissi, Project Officer

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ABSTRACT

Environmental and occupational health effects associated with exposures to various chemicals are a subject of increasing concern. One recently developed methodology for assessing the health impacts of various chemical compounds involves the classification of similar chemicals into risk-assessment categories (RACs).

This report reviews documented human health effects for a broad range of pollutants, classified by RACs. It complements other studies that have estimated human health effects by RAC based on analysis and extrapolation of data from animal research.

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INTRODUCTION

Introduction to Larger Project and RAC Concept

The U.S. Environmental Protection Agency (EPA) is developing methods to assess health and environmental risks of complex technologies producing a diverse range of pollutants. Many of these pollutants are unregulated and have relatively undefined effects. Assessments must encompass exposure via air, water, and food chains. In addition to estimating risk to humans and the environment, the program will help summarize the directions of present research and define specific research needs for an associated biomedical and environmental research effort.

An adequate chemical-by-chemical health effects risk assessment is precluded because of the vast number of chemicals involved, the inability to characterize these compounds fully, the fact that many are chemically transformed in the environment, and gaps in toxicological information. To come to grips with this problem, the concept of Risk-Assessment Categories (RACs) was developed (4). This approach groups compounds by chemical structure and other characteristics. Criteria used for the grouping and the current listing of 38 RACs are included in an appendix.

Within the context of the RAC approach, methods were developed to assess health risks using both animal and human data. All health risks are eventually to be considered, but the initial effort, based on animal studies, focused on cancer risks (5-7).

Overall program objectives involve quantifying: 1) emissions to various media by RAC; 2) environmental transport, dispersion, and population exposure through various media; and 3) health impact. The first two steps are largely being carried out at Oak Ridge National Laboratory.

Purpose and Objectives of This Effort

This review surveys health effects in man of exposure to a broad range of pollutants organized by RAC. Because of limitations on the kind of studies that can be done, human data cannot generally be as definitive as animal or cellular level experimental results. Since the results are to be applied to man, it is important that all direct observations in man be considered. The human information also supplements results of animal data in the information used to develop dose-response functions for risk assessment.

About the Report

The report is organized by RAC. Since these categories are not included in computerized bibliographic data sources, a literature review had to be based on individual compounds, and the results then organized by RAC. Some RACs are single substances (e.g., formaldehyde and benzene). Others are groups with relatively few members (e.g., aliphatic hydrocarbons with four or less carbons and radionuclides in the coal fuel cycle). In these categories, all member compounds were considered. Still other RACs are, for practical purposes, open ended (e.g., alkyl derivatives of polycyclic aromatics). For these categories, example compounds provided in the EPA listing (see Appendix) were considered. In addition, various lists of synfuel-related compounds were used to identify compounds of interest which were then classified by RAC. Lists of possible carcinogens were also used so as not to miss any potential carcinogenic properties in a RAC. Chemical Abstract Service (CAS) numbers were determined for each substance to ease computer searches.

Computerized bibliographic searches were made on Toxline, Medline, Registry of Toxic Effects of Chemicals (RTEC), and the Toxicology Data Bank. These searches identified articles linking the substances with human health effects through key words such as occupational health, epidemiology, etc. Searches were made by CAS number to avoid missing citations using various names for the same compound. The initial set of computerized searches was made in the summer of 1982 and updating searches were made in June-August, 1983.

Where available, authoritative review articles were used as the source of information. Other review sources included EPA and National Institute of Occupational Safety and Health (NIOSH) documents such as air quality criteria documents. Standard texts such as Proctor and Hughes (9), Gosselin et al. (2), Patty (8), and Sax (11) were used extensively. Other general sources included the Merck Index (12), the Encyclopedia of Chemical Technology (3), the ACGIH TLV Documentation Manual (1), and the National Toxicology Program 2nd Annual Report on Carcinogens (10). Sources identified in computerized searches were used for updating. Most of the updated information was based on abstracts. Original research articles were viewed only if abstracts did not provide clear or sufficient information.

Physiologic effects of chemicals on any organ system were considered using epidemiological and clinical studies on humans. Late in the study, experimental data using human cells in vitro were also included for some RACs. These add information on metabolic mechanisms involved in the action of given chemicals. In general, animal studies were not drawn upon, although some specific data or comparative human and animal studies were occasionally included. Animal studies were the focus of a separate report in the case of carcinogenic effects (7). The animal literature for other kinds of effects will be the subject of future work.

While individual substances within each RAC are related, there are variations of both kind and magnitude in their health impact. For example, several RACs contain compounds that are carcinogens, as well as other compounds that are not carcinogens or for which carcinogenicity is unknown. In each RAC review, effects of individual compounds are discussed and a summary checklist developed. These checklists are further summarized in Chapter 2 to provide a listing of the kinds of effect produced within each RAC.

While no rigid format has been imposed on the RAC reviews, a general list of factors to be considered was developed. Among these are: 1) a description of the RAC, with the range of individual compounds included, usual state, and other pertinent physical and chemical properties; 2) general status of knowledge of human effects for substances in the RAC; 3) background levels of exposure, threshold limit values (TLVs), short-term exposure limits (STELs) (1), and standards; 4) kinds of effects; 5) mechanisms; 6) dose-response information; and 7) references. Of course, many of these factors are not applicable or are unknown for some RACs. Some factors more important for particular RACs have been given greater emphasis.

In a number of instances, synergistic health effects have been reported between different pollutants and there are probably many potential synergistic effects not yet discovered. Studies of these effects are occasionally mentioned, but their detailed analysis is beyond the scope of this report. The number of possible combinations are extensive and a comprehensive approach to this problem has not yet been developed.

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CHAPTER 2 OF HUMAN HEALTH REVIEW

SUMMARY

The available human literature on health effects of exposure to pollutants is reviewed by RAC in the following chapters. The summary table which follows, consolidates the kinds of effects found by RAC. Each "X" indicates evidence found in the human literature that at least one substance reviewed within that RAC affects that organ system. A question mark, "?," indicates: 1) there is some evidence of effect in animal literature and a corresponding effect is expected in man, but no direct human evidence exists, 2) an effect is hypothesized based on experience with similar compounds, or 3) there are inconclusive human data. In the last case, the decision to use an "X" or a "?" was judgmental.

The table is more a guide to the scope of the report than a presentation of independently useful information. An effect may be based on one substance in an RAC containing many other substances which do not produce that effect. The reader should refer to the individual RAC reviews following to determine the context of the indicated effect as well as to discover the extent of any mechanistic or dose-response information.

In general, reliable, quantitative dose-response information based on human data is scarce. The kinds of experiments that can be done are limited and numbers are necessarily small in human experimental studies. Observational studies are subject to countless difficulties in interpretation due to uncontrolled factors. Epidemiological studies usually involve a broad mix of concurrent exposures, making associations with a particular agent difficult.

Nonetheless, the human literature is important. It represents direct observation in humans when estimating health effects. It can best be used together with animal data. Human literature can suggest animal experiments, it can be used to verify and calibrate dose-response information derived from animal data, and it can suggest specific additional human studies which may be useful.

RAC	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
	SYSTEM											EFFECT							
1. Carbon Monoxide	X				X				X				X		X				X
2. Sulfur Oxides		X						X									X		X
3. Nitrogen Oxides	X	X			?			X		?			?				X	X	
4. Acid Gases	X	X	X		X	X		X		X							X		X
5. Alkaline Gases		X	X			X		X	X								X		
6. Hydrocarbon Gases			X						X									X	X
7. Formaldehyde		X	X					X	X			?			?	X	X		
8. Volatile Organochlorines	X	X	X	X	X	X	X	X	X	X	X	X	?	X	X		X	X	
9. Volatile Carboxylic Acids		X	X			X	X	X									X		
10. Volatile O&S Heterocyclics		X	X			X	X	X	X		X	?					X		
11. Volatile N Heterocyclics	X	X	X		X	X	X	X	X		X	?		?			X		
12. Benzene	X		X		X	X			X			X					X	X	
13. Aliphatic/Alicyclic Hydrocarbons			X			X		X	X								X	X	

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC	SYSTEM											EFFECT							
	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
14. Mono/Diaromatic Hydrocarbons	X	X	X		X	X	X	X	X		X		?	?			X	X	
15. Polycyclic Aromatic Hydrocarbons		X	X			X	?	X				X		X	?	X	X		
16. Aliphatic Amines			X					X									X		
17. Aromatic Amines			X		X		X					X					X		
18. Alkaline Nitrogen Heterocyclics		X	X					X	X			?					X		
19. Neutral N, O, & S Heterocyclics																X			
20. Carboxylic Acids		X	X			X		X								X	X		
21. Phenols	X	X	X		X	X	X	X	X	X	X			X	?	X	X	X	
22. Aldehydes and Ketones (excluding formaldehyde)	X	X	X		X	X	X	X	X		X						X	X	
23. Nonheterocyclic Organo Sulfur	X	X	X		X	X	X	X	X	X	?	?			X		X	X	
24. Alcohols	X	X	X		X	X	X	X	X	X	X		X	?	X		X	X	
25. Nitroaromatics					X	X			X	X	X	?		X					
26. Esters			X					X	X								X	X	

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC	SYSTEM											EFFECT							
	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
27. Amides			X					X				?	?				X		
28. Nitriles		X	X		X	X		X	X		X	X		X			X	X	
29. Tars		X	X				X					X				X	X		
30. Respirable Particles	Included in other RACs																		
31. Arsenic	X	X	X	X	X	X	?	?	X	X	X	X	?				X		
32. Mercury		X		X		X	X	X	X				X		X		X		
33. Nickel	X	X	X			X		X				X				X	X		
34. Cadmium	X	X	X	X	X	X	X		X	X	X	?		?	?		X		
35. Lead	X			X	X	X	X		X			?	?		?		X		
37. Radioactive Materials												X		X					

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

CHAPTER 3

REVIEW OF INDIVIDUAL RISK-ASSESSMENT CATEGORIES

RAC #1 - CARBON MONOXIDE

Overview

Carbon monoxide (CO) is produced by the incomplete combustion of hydrocarbons; it is a constituent of flue gas from coal, oil, and natural gas furnaces and of automobile exhaust. It is a constituent of low- and medium-Btu synthetic gas.

Acute Effects

Effects of CO in humans at high levels are well known (3). These levels are occasionally experienced in occupational settings, in homes with unvented heaters, and in automobiles, buses, or trucks, with faulty exhaust systems. At these levels, CO acts principally by forming a complex with the hemoglobin molecule (carboxyhemoglobin), reducing the oxygen-carrying capacity of the blood as well as reducing the rate of dissociation of oxyhemoglobin to tissue. Because of its sensitivity to lack of oxygen, the brain is the most critical organ affected. Dose-response functions are well-defined based on occupational epidemiology and clinical experiments.

At lower concentrations (<50 ppm), quantitative dose-response functions are more uncertain, although evidence of effects was sufficiently compelling to justify a National Ambient Air Quality Standard of 10 ppm (10 $\mu g/m^3$) for an 8-hour averaging period. Effects have been repeated on vigilance, vision function and perception, and psychomotor performance. These may be mechanisms behind suggestions of increased motor vehicle injury and fatality rates during high CO periods alone or in combination with CO levels from faulty exhaust systems (2).

Chronic Effects

Effects of low-level CO in ambient air have been extensively reviewed (1). Cardiovascular abnormalities have been reported in association with CO exposure. Some epidemiologic studies have suggested increased mortality from myocardial infarction associated with high ambient CO concentrations, although similar studies have shown no effect. Effects of CO on pulmonary function have also been reported.

Low (<50 ppm) concentrations of CO may put principal risk on particularly sensitive groups: fetuses, persons with cardiovascular or CNS defects, sickle cell anemia, the young and the elderly, those taking certain drugs, and those at high altitude. At high altitude the concentration of oxygen in air is lower (e.g., 18% less in Denver than at sea level). Thus, similar concentrations of CO will have greater impact at high altitude. The effect of CO and altitude seem to be additive, although CO hypoxia and hypoxic hypoxia are not equivalent.

CO concentrations in the air are relatively easy to measure, and actual human exposure can be estimated by direct or indirect measurements of carboxyhemoglobin levels in blood (4-6).

A TLV of 50 ppm and an STEL of 400 ppm have been set for CO. NIOSH recommends a 35-ppm TWA and a 200 ppm STEL to protect workers with chronic heart disease.

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RAC 1	SYSTEM											EFFECT							
CARBON MONOXIDE	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Carbon Monoxide CO	X				X				X				X		X				X

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #2 - SULFUR DIOXIDE (SO_2)

Overview

Sulfur dioxide is formed when materials containing sulfur are burned (soft coal, high sulfur oil, etc.) and is thus an important air pollutant (1). It is used in smelting operations, paper manufacturing, as a bleaching, disinfecting, and fumigating agent, as a reducing agent, and as a food additive and preservative (1).

Acute Effects

Sulfur dioxide rapidly forms sulfurous acid on contact with moist mucous membrane, thereby explaining its prominent biologic effect of severe mucous membrane irritation. In concentrations above 20 ppm, marked irritant effects such as choking and sneezing occur. Exposures of 50 to 100 ppm cause irritation of the nose and throat, resulting in rhinorrhea and cough; and may lead to reflex bronchoconstriction and an increase in bronchial mucous secretion with increased pulmonary resistance to air flow. These changes may be clinically manifested as high pitched rales and a tendency to prolongation of the expiratory phase of respiration. In human experimental studies, subjects inhaling SO_2 through the mouth exhibited varying degrees of bronchoconstriction, as measured by increased pulmonary flow resistance (9,10).

Exposures to 400 to 500 ppm are life threatening when inhaled in a confined space and will probably result in asphyxia. In exposures that are high but not sufficient to cause asphyxia, a chemical bronchopneumonia may develop which can be fatal.

Sulfur dioxide gas is irritating to eyes and may produce burning discomfort and lacrimation, but actual eye injury from exposure is rare (7). However liquid SO_2 from pressurized containers has caused severe corneal burns (8). In brief exposures of 1 ppm, no effects were seen; 5 ppm caused a 40% increase in pulmonary flow resistance; and 13 ppm caused a 73% increase in pulmonary flow resistance (8).

Chronic Exposure

Chronic exposure to SO_2 is widespread in industry. Most exposures have occurred with chemical mixtures containing SO_2. Symptoms associated with low chronic exposures are: respiratory tract irritation leading to cough, epistaxis, chest constriction, and hemoptysis. In addition, nasopharyngitis, alteration in the senses of smell and taste, and increased sensitivity to other irritants may occur from chronic occupational exposures (2, 10). Some sensitive individuals have developed occupational asthma after prolonged SO_2 exposure (2).

Some epidemiological studies have found that in areas of increased SO_2 and NO_2 pollution, decreased ventilatory function was observed in children and adults. There is also evidence that children living in areas with high atmospheric SO_2 and NO_2 pollution have increased incidence of pulmonary problems (5, 6).

SO_2 in itself is not known to be a carcinogen, but Lee and Fromeni have suggested that SO_2 may be a respiratory tumor promotor when combined with high arsenic exposures (3). Laskin et al. found an increased incidence of squamous cell carcinoma when SO_2 at chronic exposure levels of 3.5-10 ppm were combined with inhaled benzo[a]pyrene (1).

A TLV of 2 ppm and an STEL of 5 pm have been set for SO_2.

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RAC 2	SYSTEM											EFFECT							
SULFUR OXIDES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Sulfur Dioxide SO_2		X						X									X		X

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #3 - NITROGEN OXIDES

The term nitrogen oxides (NO_x) refers to a family of compounds which typically include: nitric oxide (NO) and nitrogen dioxide (NO_2), the two most important pollutants in the lower atmosphere; nitrous oxide (N_2O) which occurs naturally in unpolluted air; symmetrical nitrogen trioxide (NO_3); unsymmetrical nitrogen trioxide (O-O-N-O); dinitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4), and dinitrogen pentoxide (N_2O_5) (10). NO and NO_2 are the principal anthropogenically produced oxides of nitrogen and will be addressed in this RAC. NO_2, the more irritating and toxic compound, will be given the most attention.

Overview

Most of the NO_x produced is initially in the form of NO which is quickly oxidized to NO_2. NO, a colorless and odorless gas, is favored during high temperature combustion and is formed by interaction of the nitrogen content of fuel with ambient nitrogen and oxygen.

Nitrogen dioxide is a reddish-brown gas, formed by the action of nitric acid on reducing agents, by the combustion of nitrogenous organic material, and by the oxidation in air or oxygen of nitric oxide. Some sources of industrial emissions of NO_2 are: reaction between nitric oxide and organic materials; metal cleaning processes; electric arc welding; electroplating, engraving, and photographic operations; dynamite blasting; diesel exhaust; and other combustion processes. High concentrations of NO_2 are frequently present in silos where ensilage is stored. Exposure can occur both in and out of doors. The highest and most variable outdoor NO_2 levels are known to be in urban areas because of traffic congestion and industrial activity. Indoor sources such as gas appliances (cooking, kerosene space heaters, dryers, etc.) contribute significantly to high exposures. Cigarette smoke also contains NO and NO_2 and can actively or passively be a significant source of exposure.

Acute Effects

Very high exposures to NO_2 (about 300 ppm) occurring during industrial accidents can cause rapid death (10). Exposure to concentrations in the 150- to 200-ppm range causes severe respiratory distress, and death is likely after 2 to 3 weeks, always by bronchitis fibrosa obliterans. Exposures to concentrations of 25 to 100 ppm cause reversible bronchiolitis, bronchitis, or bronchial pneumonia, usually followed by complete recovery.

Episodic or peaking concentrations of NO_2 (possibly augmented by NO), have been shown to cause immediate and short-term irritation to sensitive subgroups of the population such as asthmatics and individuals recovering from acute respiratory infections. Clinical studies of the short-term effects of NO_2 on human volunteers have been conducted on asthmatics, bronchitics, and healthy subjects. Functional impairment was not observed in healthy subjects or patients with bronchitis at or below 1.5 ppm NO_2. These studies have generally shown that the sensitivity of asthmatics to irritants such as other air pollutants or cold air can be heightened by short-term concentrations of 0.5 ppm NO_2 or higher (7). Recovery from these effects tends to be rapid, and it is not known whether repeated exposures of this kind have any cumulative effects or predispose the lungs to permanent damage. In one controversial study, heightened sensitivity (airway reactivity) or irritation to a bronchioconstrictive aerosol has been shown for some asthmatic patients exposed to NO_2 concentrations as low as 0.1 ppm (11). One study reported healthy adults to be unaffected by acute exposure of up to 5 ppm (1A), whereas another study found sensitivity in healthy adults to be heightened by concentrations as low as the current outdoor ambient standard of 0.05 ppm NO_2 (14).

Chronic Effects

Chronic exposure to lower concentrations of NO_2 has been associated with increased occurrence of acute respiratory infections in infants and children. Some scientists have hypothesized that repeated low-level exposures are also associated with chronic lung disease and increased "aging" of the lung in adolescence and adulthood (2, 3, 5).

Epidemiological studies of populations of children exposed to NO_2, primarily indoor air pollution, confirm laboratory findings of reduced resistance to respiratory infection in exposed animals (8, 9, 13). Children exposed to additional quantities of NO_2 (and possibly NO) from gas combustion in stoves — in particular, children under the age of two — show significantly greater incidence of acute respiratory illness and changes in lung function than their counterparts living in homes with electric stoves. More recently, investigators have expressed less certainty concerning association between indoor exposure to NO_2 from gas stoves and increased respiratory illness in children (9). Recent evidence from the Harvard six-city study strengthen these later findings. The EPA estimates that repeated exposures to 1-hr average NO_2 peaks of 0.15 to 0.30 ppm may be a health problem for children under the age of two (4). Similar but less pronounced results have been obtained for adult males (6).

In addition to its having direct health impacts, NO_2 also affects sensory perception (4). It can be smelled at a concentration of 0.11 ppm, but odor detection is rapidly impaired. Impairment of dark adaptation of the eyes has been demonstrated at concentrations as low as 0.07 to 0.08 ppm (10). These concentrations are well within the normal range in ambient air.

Populations at special risk from NO_2 exposure include children and persons with existing lung dysfunction or hay fever. Children in homes with gas stoves appear to be at unusually high risk. In addition, animal studies showing increased systemic, hematological, and hormonal alterations after exposure to NO_2 suggest that persons with cirrhosis of the liver or other liver, hormonal, and blood disorders and persons undergoing certain types of drug therapies might be at special risk (4).

Although neither NO_2 nor NO has been shown to be carcinogenic, some recent evidence suggests that NO_2, either singly, in combination with NO, or together with other ambient air pollutants, may facilitate cancer cell metastasis (12).

A TLV of 3 ppm and an STEL of 5 ppm has been set for NO_2 (1). A T.. of 25 ppm and an STEL of 35 ppm has been set for NO. The National Ambient Air Quality Standard (NAAQS) for NO_2 (primary and secondary) has been set at 100 $\mu g/m^3$ annual arithmetic mean.

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RAC 3	SYSTEM											EFFECT							
NITROGEN OXIDES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Nitrogen Dioxide NO_2	X	X			?			X		X			?				X		
Nitric Oxide NO	X	?			?			X									X		
Nitrous Oxide N_2O																		X	

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #4 - ACID GASES

The two compounds reviewed in this RAC are hydrogen sulfide and hydrogen cyanide.

Hydrogen Sulfide (H_2S)

Overview. Hydrogen sulfide is a constituent of petroleum, natural gas, sewer gas, and soil. It is also a by-product of viscose rayon production and certain leather tanning processes. It is widely used as a chemical reagent in the manufacture of heavy water. Hydrogen sulfide is also a source of elemental sulfur (5).

Acute Effects. In low concentrations (50 to 200 ppm) hydrogen sulfide is primarily a respiratory and eye irritant (1, p. 225). Prolonged exposures above 250 ppm are likely to result in pulmonary edema, and exposures of 500 to 1000 ppm may cause severe respiratory distress. Concentrations above 1000 ppm are usually fatal within minutes owing to respiratory paralysis (1, 4). Even though H_2S has a recognizable disagreeable odor, olfactory paralysis occurs at levels above 150 ppm. Therefore the sense of smell may not be a good indicator of the presence of high atmospheric levels of H_2S (4).

Subjects exposed to low levels of H_2S have reported various Central Nervous System (CNS) symptoms such as headache, nausea (with occasional vomiting and diarrhea), dizziness, confusion, and weakness of the extremities. If exposure continues, unconciousness will eventually result (7-9). Survivors of acute toxic episodes sometimes show neurologic sequelae such as amnesia, tremor, neuroasthenia, disturbances of equilibrium, and, in rare instances, brain stem damage.

Exposures to levels above 50 ppm can produce pain in the eyes, conjunctivitis, lacrimation, and photophobia. In prolonged exposures keratoconjunctivitis ("gas eye") may occur. This is a common occurrence among tunnel, caisson, and sewer workers. It manifests itself several hours or days after exposure as a scratchy irritating sensation with tearing or burning of the eye. In more serious exposures, vesiculation of the corneal epithelium may occur (4, 8).

Direct contact with the skin may produce erythema and pain. H_2S can also penetrate the skin and cause toxic symptoms in those exposed to low concentrations over long periods of time.

Chronic Effects. In a study by Bernardini et al. (2), workers exposed to H_2S exhibited a high incidence of upper airway inflammations. Gastrointestinal complaints were common, and erosion of dental crowns was observed (2). Other effects of chronic exposures include headache, eye symptoms (irritation, tearing), digestive disturbances, sleep disturbances, cardiac arrhythmias, and general disabilities (7-9).

A TLV of 10 ppm and an STEL of 15 ppm have been set for H_2S based on the finding that eye irritation has been reported at 20 ppm (1).

Hydrogen Cyanide (HCN)

Overview. Hydrogen cyanide is used as a chemical reagent in the manufacture of synthetic fibers, plastics, cyanide salts, and nitrates. It may be produced during the refining of petroleum, electroplating, metallurgy, and photographic development (1). Hydrogen cyanide is used as a fumigant and traces of HCN are found in tobacco and various foods (1).

Acute Effects. In acute doses above 100 ppm, cyanide acts as a protoplasmic poison combining with methemoglobin to form cyanmethemoglobin, causing death through asphyxiation. Suspension of tissue oxidation lasts only while cyanide is present in the system, and its effects are reversible upon removal.

Various physiologic responses to HCN concentrations include the following (1, 3, and 6):

0.1-0.9 ppm	no effect
0.2-5.0 ppm	odor threshold
10 ppm	threshold limit value
4.5-18 ppm	headache and vertigo
18-36 ppm	slight symptoms after several hours
45-54 ppm	tolerated 1/2 to 1 hour without effect
110-135 ppm	fatal 1/2 to 1 hour after exposure or life threatening

135 ppm	fatal within 30 minutes
181 ppm	fatal within 10 minutes
270 ppm	immediately fatal

Ingested, the oral lethal dose is probably less than 5 mg/kg body weight. Less than 7 drops can constitute a fatal dose for a 70-kg person (3).

Chronic Effects. Workers exposed to HCN in the electroplating industry have complained of dermatitis and irritation of the nose, occasionally leading to obstruction, bleeding, and perforation of the nasal septum. Reports of chronic intoxication to HCN exist, but they are limited and based on subjective symptoms such as headache, weakness, changes in taste and smell, throat irritation, vomiting, dyspnea, lachrymation, abdominal colic, precordial pain, and nervousness. Enlargement of the thyroid gland has been observed by a few investigators in workers using cyanide salts. However, many investigators deny any HCN chronic effects and reports of chronic cyanide poisoning are rare (7-9).

A TLV of 10 ppm has been set for hydrogen cyanide.

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RAC 4	SYSTEM											EFFECT							
ACID GASES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Hydrogen Sulfide H_2S	X	X	X			X		X									X		X
Hydrogen Cyanide HCN			X		X			X		?							X		X

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #5 - ALKALINE GASES

Ammonia is the only gas considered under RAC #5. Ammonia is a colorless gas that is irritating to eyes, respiratory tract, and skin. Exposure to high air concentrations (2500 to 6500 ppm) can produce fatal respiratory effects, while in an occupational setting, 4 to 29 ppm produced "barely noticeable" irritation (5, p. 101). Carson et al. (1) conclude that 0.32 mg/m^3 is the lowest concentration at which effects have been observed in human experimental exposure. These effects include decreased eye sensitivity to light and changed cortical activity. They report experiments in which some people could perceive odor at slightly higher levels (0.45 mg/m^3).

Ingestion of ammonia solutions produce effects characteristic of corrosive alkalis and even small amounts (a few ml) have been recorded as a fatal oral dose, although a few hundreds of ml of 5 to 10% solution have been tolerated (2).

Gosselin (2, p. 20) claims ammonia does not produce signs of systemic intoxication and has no significant cumulative effect. Biologic defects can cause accumulation of ammonia leading to ammonia toxicity (4). Some cumulative effects have been reported, however. Ferguson et al. (3) observed dose-dependent changes in respiratory function in a six-week experiment with concentrations of 18 to 72 mg/m^3. A number of epidemiological studies have reported adverse effects of chronic exposure to low airborne concentrations of ammonia (e.g., hyperemia of the conjunctiva and eyelids, headache, loss of appetite, chronic fatigue, and complaints of various respiratory disorders). Most studies, however, were of populations with concurrent exposure to other irritating air pollutants (e.g., nitrogen dioxide), had poor ammonia exposure estimates, and lacked adequate control populations or even adequate characterization of the population studied (4, pp. 7-25).

Ambient air concentrations of ammonia are much lower than those at which any effects have been observed. Rural ground-level concentrations exhibit strong seasonal variations due to bacterial activity but range from 7 to 20 $\mu g/m^3$ (10 to 30 ppb). Urban ammonia concentrations are higher, 10 to 60 $\mu g/m^3$ in the U.S. and over 100 $\mu g/m^3$ in some European cities (4).

Currently available evidence is inadequate even to conclude that there are human health effects of small incremental exposures to ammonia at these low ambient levels.

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RAC 5	SYSTEM											EFFECT							
ALKALINE GASES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Ammonia NH_3		X	X			X		X	X								X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #6 - HYDROCARBON GASES

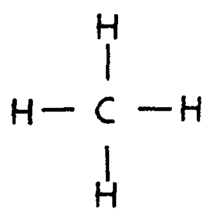
Hydrocarbon gases include aliphatic hydrocarbons with the carbon chain ranging from C_1 to C_4. They are divided into alkanes (carbon chains with no double bonds), alkenes (one or more double bonds), and alkynes (triple bonds). Aliphatic hydrocarbons are all colorless flammable gases.

No adverse health effects were found for this group of compounds in subjects exposed to low atmospheric levels of hydrocarbon gases. High concentrations of hydrocarbon gases can dilute the oxygen in the air to levels which will not support life, thereby causing asphyxia. In RAC #6, the following compounds were reviewed.

Alkanes (Saturated Hydrocarbons)

Alkanes occur as constituents of natural gas. Beginning with propane through octane-saturated hydrocarbons show increasingly strong narcotic properties.

Methane CH_4

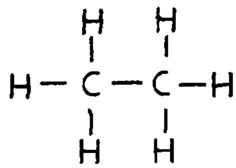


Methane is widely distributed in nature. American natural gas is composed of 65 to 95% of methane.

Methane is found in coal deposits and is released during mining operations. It is highly flammable and can form explosive mixtures in underground mining operations. Methane gas produced by the decomposition of organic matter is called "marsh gas" when it is produced during the decay of vegetation in stagnant waters. Methane is the principal constituent of natural gas. Relatively small amounts of methane are produced as a by-product of the petroleum process. Its largest use is in the production of ammonia, methanol, and acetylene.

Methane in high concentrations is a simple asphyxiant.

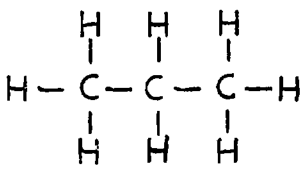
Ethane (Bimethyl; Dimethyl) CH_3-CH_3



Ethane is also a constituent of natural gas (about 0.8 to 9%). Its most important commercial use is in the production of ethylene. It has been used as a feedstock for the production of vinyl chloride (3, p. 909).

Ethane can be tolerated in relatively high concentrations of inspired air without producing systemic effects. If concentrations are high enough to dilute or exclude oxygen, however, asphyxia will result.

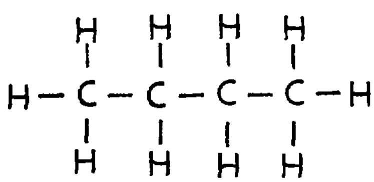
Propane (Dimethyl Methane) CH_3-CH_2-CH_3



Propane is used in the production of ethylene, and as fuel gas (usually liquefied in pressurized vessels) sometimes mixed with butane. Propane is also used in organic syntheses and as a refrigerant.

Brief exposure to 10,000 ppm causes no symptoms in man. Odor is not detectable below 20,000 ppm. A concentration of 100,000 ppm (10%) will produce slight dizziness (5, 6). At very high concentrations, propane is an asphyxiant (1, 2).

Butane C_4H_{10}



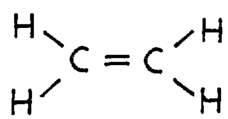
Butane has two isomeric forms: n-butane CH_3-CH_2-CH_2-CH_3 and isobutane $(CH_3)_3CH$. It occurs in petroleum and in natural gas. It is a component of high octane liquid fuels. It is used as a food additive and as a propellant for aerosols.

Butane, like other homologs in the straight chain hydrocarbons, is relatively nontoxic. Butane has simple asphyxiant, irritant, and anesthetic properties at high concentrations. No known adverse health effects have been demonstrated from low level exposures. Subjects exposed to 10,000 ppm (1% concentrations) reported feeling drowsy, but no evidence of other systemic effects were noted (1, p. 51).

Because of their extreme flammability, butanes necessitate handling and storage precautions. A TLV of 800 ppm has been recommended for butane.

Alkenes (Hydrocarbons With Double Bond)

Ethylene (Ethene) $CH_2{=}CH_2$

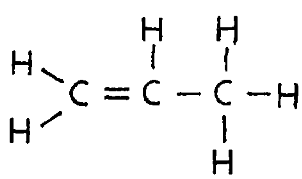


Ethylene is a colorless flammable gas. It is a compound in illuminating gas, and a by-product of coke oven gas. In the chemical industry ethylene is a "feedstock" for a variety of petrochemical products, such as olefins. In agriculture it has been used as a ripening agent for fruits and vegetables and as a herbicide for witchweed (3, p. 423).

Ethylene is nonirritating to the eyes and respiratory system. It quickly diffuses when released into the atmosphere. At very low concentrations, 2.7%, a flammable mixture is formed (3, p. 422).

No adverse long-term health effects have been reported from the temporary inhalation of low levels of ethylene gas. At high levels, it is a simple asphyxiant. Skin contact with liquid ethylene may cause frostbite (4).

Propylene (Propene) $CH_2{=}CH{-}CH_3$

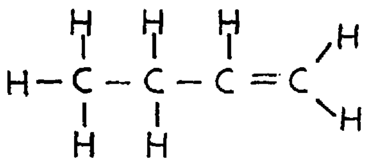


Propylene is a flammable gas obtained from petroleum oils during gasoline refining. It can also be obtained by dehydrogenation of propane.

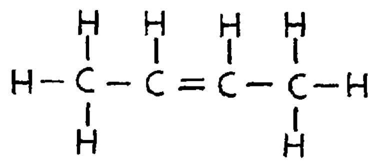
Propylene is used in polymerized form as polypropylene, a thermal plastic material, and as a raw material in the manufacture of other chemicals.

Propylene is a simple asphyxiant. High concentrations cause unconsciousness.

<u>Butylene (Butene)</u> C_4H_8



α

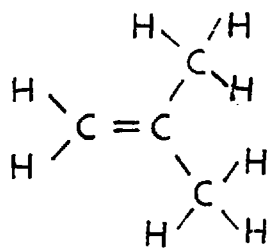


β

Butylene occurs in two isomeric forms as 1-butene (α -butene) CH_3-CH_2-CH=CH_2 and 2-butene (β -butene) CH_3-CH=CH-CH_3. Both forms are gases and occur in coal gas and in petroleum oil.

No known adverse health effects have been reported in the literature from low level exposures to 1-butene and 2-butene. In high concentrations they act as weak anesthetics and asphyxiants. Because of flammability hazards, the maximum permissible workroom atmosphere concentration for either compound is 4000 ppm (4).

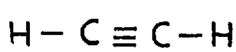
<u>Isobutylene (Isobutene; 2-Methyl Propane)</u> CH_2=C(CH_3)$_2$



Isobutylene is a highly flammable gas which forms an explosive mixture when mixed with air and oxygen. It is obtained from refinery streams. It is primarily used to produce butylene polymers. In high concentrations isobutylene is a weak anesthetic and an asphyxiant.

Alkynes (Hydrocarbons With Triple Bond)

<u>Acetylene (Ethyne)</u> CH≡CH

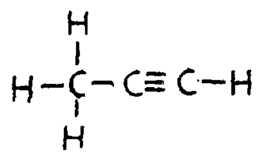


Acetylene is a highly flammable gas manufactured from calcium carbide and water. It is used as an illuminant, in oxyacetylene welding and cutting metals, and in the manufacture of acetaldehyde.

Acetylene in high concentrations acts as an asphyxiant. Patty reports that subjects inhaling 100,000 ppm (10% concentration) showed slight intoxicant effects. Marked intoxication has been reported at 200,000 ppm (20% concentration), incoordination at 300,000 ppm (30% concentration), and unconsciousness after a 5-minute exposure to 350,000 ppm (35% concentration). Symptoms of acetylene gas exposure are readily reversible once the person is removed from the contaminated atmosphere.

Dizziness, headache, and mild gastric symptoms have been reported by subjects exposed to acetylene vapors, but these symptoms are thought to be due to the impurities found in commercial acetylene (4,7).

Propyne (Methyl Acetylene) $CH_3C{\equiv}CH$



Propyne is a colorless gas with a sweet odor.

Experiments on animals indicate that methyl acetylene has a low toxicity. A TLV of 1000 ppm has been suggested (1).

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RAC 6	SYSTEM											EFFECT							
HYDROCARBON GASES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Methane CH_4																			X
Ethane CH_3-CH_3																			X
Propane $CH_3-CH_2-CH_3$									X										X
Butane C_4H_{10}									X									X	X
Ethylene $CH_2=CH_2$			X						X										X
Propylene $CH_2=CH-CH_3$									X										X
Butylene C_4H_8									X									X	X
Isobutylene $CH_2=C(CH_3)_2$									X									X	X
Acetylene $CH{\equiv}CH$									X									X	X
Propyne $CH_3C{\equiv}CH$																			X

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #7 - FORMALDEHYDE

Formaldehyde (HCHO) is a colorless gas with a pungent odor highly irritating to the eyes, nose, and upper respiratory tract. Recent concern with formaldehyde stems from symptoms reported by people exposed to outgassing of formaldehyde from urea-formaldehyde foam insulation and phenol-formaldehyde resins in particleboard or plywood.

Extensive reviews were carried out on the health effects of formaldehyde by the National Academy of Sciences Committee on Aldehydes (13) and by the Midwest Research Institute (5) in 1981. This report relies primarily on those reviews. There is a substantial amount of human literature on irritant and respiratory effects of formaldehyde. Although no quantitative dose-response function for such effects is in use, sufficient information is available for its development if needed. Several studies have been initiated, but insufficient human data are currently available on carcinogenic or reproductive effects for the development of dose-response functions.

Formaldehyde is a skin irritant and skin sensitizer. Allergic contact dermatitis from contact with formaldehyde resin or formaldehyde dust is relatively common (1). In general, no other effects have been reported in humans below airborne concentrations of 0.05 ppm. Beginning at this level, changes in laboratory tests of neurophysiologic effects (EEG alterations and changes in the sensitivity of the eye to adapt to light) have been observed. Some people can perceive the odor of formaldehyde at this concentration, and there are reports of eye irritation at 0.05 ppm, but, in general, odor perception and nose, throat, and bronchial irritation begin at about 1 ppm. It has been estimated that 10 to 20% of the population is sensitive to concentrations of formaldehyde below 1 ppm and bronchial asthma has been reported after prolonged exposure to the vapors of formaldehyde. Severe pulmonary reactions (pneumonia, pulmonary edema) occur at concentrations exceeding 50 ppm. The severity of the effect seems to be dose related (13). Evaluation of pulmonary function by spirometry and nitrogen washout suggests that exposure to formaldehyde causes bronchoconstriction (3). Inhalation exposure of workers to phenol, formaldehyde, and melamine adhesives resulted in a significant increase in high-density lipid cholesterol (14).

Ambient outdoor concentrations of formaldehyde are usually less than 0.05 ppm and rarely exceed 0.1 ppm. Over 11 million people live in homes with either urea-formaldehyde foam insulation or particleboard made with urea-formaldehyde resins. The concentrations of formaldehyde most commonly reported in such homes range from 0.1 to 0.2 ppm (13). Thus, additional exposure to people with such backgrounds might increase irritant and respiratory effects.

The National Academy of Sciences Committee on Aldehydes reported no evidence of formaldehyde causing cancer or reproductive effects in man, but production of nasal cancer in mammals and reproductive effects in nonmammalian systems have raised such concerns (2, 13).

Studies on human cells in vitro demonstrated that formaldehyde induced DNA single-strand breaks in human fibroblasts and in bronchial cells (6,7,9). Growing human fibroblasts exposed to 2 mM formaldehyde for 15 minutes showed quantitative and quantative effects comparable to those produced n x-ray dose of 100 rad (11). Formaldehyde-induced mutations and chromosomal damage were observed in human lymphoblasts and lymphocytes (8, 12). Mutations were also recognized in Salmonella typhimurium in a forward mutation assay (8-oxaguanine resistance) but not in the standard Ames test (4). Some epidemiological studies have linked formaldehyde exposure to cancers of skin, larynx, oral cavity, nasal cavity, liver, and lung, but there seems to be general agreement with the International Agency for Research on Cancer that "... epidemiological studies provide inadequate evidence to assess the carcinogenicity of formaldehyde in man." (10).

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RAC 7	SYSTEM											EFFECT							
FORMALDEHYDE	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Formaldehyde HCHO		X	X					X	X			?		?	?	X	X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #8 - VOLATILE ORGANOCHLORINES

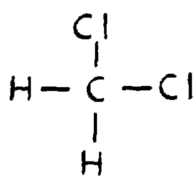
Volatile organochlorines listed in RAC #8 include chloro derivatives of methane, ethane, and ethylene. Except for vinyl chloride, all compounds in this group are used as industrial solvents. Most of them are widely used as degreasing agents in industries and as solvents in dry cleaning.

Organochlorines are in general volatile, and the major health effects are due to inhalation. They are readily absorbed, with the liver and kidneys being the main target organs.

In low chronic exposures, many have been implicated in central nervous system, kidney, and liver damage. They are all central nervous system depressants, causing anesthesia and death if exposures are high enough.

Chloro Derivatives of Methane

Methylene Chloride CH_2Cl_2 (Dichloromethane)



Methylene chloride is a colorless volatile liquid with a distinctive sweet odor. It is widely used in industry as a solvent and a degreaser, and in commercial perparations of paint removers readily available for home use. It is considered one of the least toxic of the chlorinated methanes. It accumulates slowly in adipose tissue and has a half-life elimination from the body of 6 hours (16, pp. 1-2).

Acute Effects. Since methylene chloride is metabolized in the liver to form carboxyhemoglobin (COHb), many of the acute health effects observed are due to the lowering of the oxygen content in the blood leading to neurological and cardiovascular symptoms similar to carbon monoxide toxicity. In a controlled human exposure study, a performance decrement in a tracking monitoring task was observed at 200 ppm; depression of the flicker fusion threshold and of vigilance performance was observed at 300 ppm (60). At prolonged exposures of 500 ppm, COHb levels could be reached where noticeable symptoms would develop. At 800 to 1,200 ppm, early CNS effects such as lightheadedness and dizziness may occur. At levels of 2300 ppm and above, symptomatology such as lightheadedness, dizziness, nausea, headache, tingling and numbness of the extremities, and impairment of mental alertness and coordination would develop. Ingested, a fatal dose for a 68-kg person ranges from 1/3 to 1 pint (35). Damage to the nervous system has been reported following acute exposure (16).

In liquid form, methylene chloride is mildly irritating to the skin and painful and irritating if splashed into the eyes (2, 4).

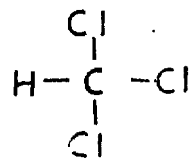
Chronic Effects. Clinical laboratory evaluation of employees occupationally exposed to methylene chloride demonstrated an increase in red cell counts, hemoglobin, and hematocrit among women but not among men exposed to approximately 475 ppm, which suggested a compensatory hematopoietic effect. A dose-related increase in serum bilirubin occurred both in men and women. However, no corresponding pattern of dose-related or hemolysis was found for other serum and blood constituents (46, 47).

No other deleterious long-term effects upon human health or performance were found in workers exposed to levels within recommended industrial criteria (5), but it is possible for exposed workers to develop increased COHb levels especially if they smoke or if there are other sources of CO in the atmosphere. It is also possible that chronic exposure to high doses of methylene chloride may be hepato and renal toxic, but no cases were reported of liver or kidney effects from chronic or acute exposures. Since methylene chloride readily crosses the placenta, it could have effects on the developing fetus.

In studies on DNA damage by haloalkanes in human lymphocytes <u>in vitro</u>, dichloromethane, chloroform, and tetrachloride gave low or negative results (50).

A TLV of 100 ppm is recommended if there is no other occupational exposure to CO in the workplace (2). The STEL of 500 ppm has been set based on data that no undesirable levels of COHb are likely to occur at this short-term exposure if there are no other sources of CO. These recommendations have to be adjusted for concurrent CO exposures (2).

Chloroform (Trichloromethane) $CHCl_3$



Chloroform is a clear, nonflammable, volatile, sweet-smelling liquid used as a raw material in refrigerant and resin production and as an extractant and industrial solvent. At one time it was used in the dry cleaning industry and it was widely used in the past as an anesthetic agent (2).

Acute Effects. Doses above 1000 ppm cause CNS symptoms such as dizziness, fatigue, and headache (4). As exposures increase symptoms become more severe, and at levels around 10,000 ppm clinical anesthesia results. Above these levels cardiovascular depression may occur leading to death from ventricular fibrillation (35).

Ingestion of liquid chloroform causes severe burning in the mouth, throat, and chest, and abdominal pain and vomiting. Depending on the amount swallowed, loss of consciousness and liver injury may occur (35). Repeated or prolonged skin contact may result in local tissue irritation and inflammation (4,51).

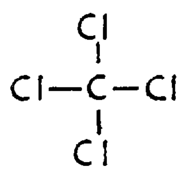
Chronic Effects. The most serious effects of repeated exposures to chloroform are liver and kidney damage (3). The chance of liver injury associated with cloroform exposure is significantly increased in alcoholics and persons with nutritional deficiencies (35). In addition, repeated low level exposures (below 100 ppm) may cause a variety of central nervous system symptoms (lassitude, mental dullness) and GI symptoms (digestive disturbances) (2, 35, 51).

The mechanism involved in chloroform toxicity is not totally clear. Laboratory studies on isolated hepatocytes suggest two phases in chloroform toxicity: 1) chloroform metabolism, and 2) lipid peroxidation (31). It was also suggested that phosgene ($COCl_2$) is the toxic intermediate in chloroform metabolism (56). Acute chloroform injury to the kidney is supposedly caused by a toxic metabolite which is most likely produced within the kidney (36). Chloroform added to incubated human plasma enhances the generation of proteolytic activity attributable to plasmin (25). Studies on trihalomethanes as initiators and promoters of carcinogenesis did not demonstrate tumor-initiating activity of chloroform; a tumor-promoting activity indicated by these results requires further confirmation (49).

From animal experiments, chloroform is suspected of being carcinogenic (52) and embryotoxic (2), but no studies were found documenting these effects on humans.

There have been few reports of occupational poisoning from chloroform, primarily because its use as an industrial solvent is limited (2, p. 90). Because of recent reports on the carcinogenicity and embryotoxicity of chloroform, a TLV of 10 ppm has been set. This is one fifth of the concentration at which organ injury was observed (2, p. 91).

Carbon Tetrachloride (Tetrachloromethane) CCl_4



Carbon tetrachloride is a heavy mobile liquid with a sweet odor (2), widely used at one time as a solvent and a degreasing agent, but because of its high toxicity it has generally been replaced by one of the less toxic volatile organochlorines. Low levels of CCl_4 have been found in water samples, and some extremely high levels have been found in urban air and in drinking water samples (5).

Carbon tetrachloride is readily absorbed into the system by ingestion and inhalation, and, to a lesser degree, by skin penetration. The chief target organs are the liver, and kidneys.

Acute Effects. Like most of the other volatile organochlorines, carbon tetrachloride is a central nervous system depressant, causing narcosis and death at high exposures. Ingested carbon tetrachloride causes a burning sensation in the mouth, esophagus, and stomach followed by gastric symptoms (initially diarrhea and later constipation). If the dose is, large enough, liver symptoms such as jaundice and liver enlargement may occur. Central nervous system symptoms such as dizziness, confusion, unconsciousness, and coma may occur depending on the amount ingested (17, 26, 48, 51).

Skin contact produces pain with erythema, hyperemia, and wheal formation, followed by vesication (44).

Chronic Effects. At low level chronic exposures (45 to 100 ppm), subjects exhibited symptoms such as gastrointestinal upset, with nausea and vomiting, and central nervous symptoms such as headache, drowsiness, and excessive fatigue. At exposures between 100 and 300 ppm, workers have demonstrated apathy, mental confusion, and weight loss (12, p. 704). Liver function abnormalities have been found in subjects chronically exposed to carbon tetrachloride, even in the absence of clinical symptoms, and chronic exposure has also been responsible for liver and kidney damage (2, p. 75). Since alcohol increases the toxicity of carbon tetrachloride, alcoholics are more likely to suffer liver damage at lower exposures (2, 5).

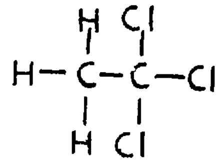
Carbon tetrachloride has produced hepatic cancers in animals, but human data on carcinogenicity are preliminary and based on isolated case reports (52, p. 73).

Carbon tetrachloride belongs to a group of chemicals which were nonmutagenic to Salmonella typhimurium, but produced morphological transformations in Syrian hamster embryo cells (4). Incubated with rat liver microsomes, CCl_4 was metabolized to potentially toxic metabolites (39).

On the basis of animal experiments which showed fatty infiltration of the liver at 10 ppm and the potentiation of carbon tetrachloride toxicity by alcohol and other industrial substances, a TLV of 5 ppm has been recommended. An STEL of 20 ppm was recommended to avoid fatigue and central nervous system symptoms (2, p. 75).

Chloro Derivatives of Ethane

Methyl Chloroform (1,1,1-Trichloroethane) CH_3-CCl_3



Methyl chloroform is a volatile clear liquid, considered among the least toxic of the industrial chlorinated solvents (35, p. 730). Since methyl chloroform readily evaporates into the atmosphere, its major route of absorption is through inhalation of the vapor (14, 24). It is estimated that for an 8-hr TWA exposure of 350 ppm (1890 ng/m^3) about 2 g will be absorbed into the body of a 70-kg man (14). Once inhaled, it is widely distributed into all organ systems, metabolized by the liver, and eliminated via the lungs, with its metabolites excreted in the urine (14). In very high doses methyl chloroform is capable of causing death due to anesthesia and/or cardiac sensitization (2, 24, 34).

Acute effects for short-term exposures (14, pp. 1-3):

14,000 - 15,000 ppm	capable of causing death due to anesthesia and/or cardiac sensitization (2)
>5000 ppm	onset of narcosis
1900-2650 ppm	lightheadedness, throat irritation
1000 ppm	disturbance of equilibrium
350-500 ppm	slight changes in perception, obvious odor
100 ppm	apparent odor threshold

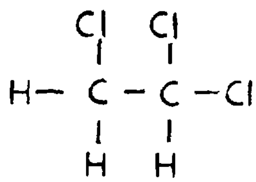
Skin exposure to the liquid form can cause irritation, pain, and blisters. Eye exposure can produce irritation, but should not cause serious injury (35, p. 731, 48, 51).

Chronic Effects. At high levels of chronic exposures (above TWA limits) cellular damage and liver function abnormalities are possible. Blood clotting changes have been reported (45, p. 9). Central nervous system symptoms such as headache, depression, dizziness, feeling of inebriation, impaired perception and reaction time, generalized weakness, ringing of the ears, unsteady gait, burning and/or prickling sensation of hands and/or feet have been reported (6, 7). Also gastrointestinal symptoms such as nausea, vomiting, and diarrhea have occurred.

Commercially available methyl chloroform may have a weak mutagenic and carcinogenic effect, as observed in laboratory experimentation (14, pp. 1-3 to 1-4), but this may be due to impurities that may be found in 1,1,1-trichlorethane such as vinylidene chloride and other stabilizers (30).

No adverse effects have been reported with concentrations likely to be encountered in the workplace. A TLV of 350 ppm has been set to prevent anesthetic effects and objectionable odor, and an STEL of 450 ppm is recommended to protect against anesthesia.

<u>1,1,2-Trichloroethane (Vinyl Trichloride)</u> $CH_2Cl-CHCl_2$



1,1,2-Trichloroethane is a colorless nonflammable liquid with a sweet odor. Because of its high toxicity, it has only limited use in industry, mainly as a solvent for fats, resins, etc. (2, p. 406), and as a chemical intermediate in the production of vinylidene chloride.

Exposure to 1,1,2 trichloroethane occurs mainly through inhalation of the vapors.

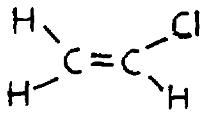
Acute Effects. In high doses, 1,1,2-trichloroethane depresses the central nervous system, causing narcosis and death from respiratory arrest. In lower concentrations, it is irritating to the eyes and nose (2, p. 406). It has a defatting action on the skin and can cause local skin irritation with possible blistering and burning.

Chronic Effects. 1,1,2-Trichloroethane is assumed to be toxic to the liver and kidneys on the basis of animal experimentation (43). Because of its limited use in industry, there are no known cases of human intoxication or chronic systemic effects from industrial exposures (48, 51, 54).

A TLV of 10 ppm and an STEL of 20 ppm has been set based on the toxicological resemblence to tetrachloroethane and by analogy with the TLV for chloroform (2, p. 406).

Chloro Derivatives of Ethylene

Vinyl Chloride (Chloroethene) CH_2=CHCl



Vinyl chloride monomer (VCM) is a colorless highly flammable gas with an ether-like odor, which becomes a liquid when pressurized. The chief use of vinyl chloride in industry is as a raw material (i.e., monomer) in the manufacture of polyvinyl chloride (PVC) (2, p. 427). In the public sector, small quantities of vinyl chloride may be ingested through water supplies and in food supplies from the migration of unconnected (unpolymerized) monomer PVC pipelines or food packaging, respectively (5).

Since it is a gas at room temperature, the most common route of exposure is through inhalation (2, p. 428). It is rapidly absorbed through the lungs and widely distributed through lipid-rich tissue.

Acute Effects. In high doses (8,000 to 10,000 ppm), VCM acts as a Central Nervous System depressant. After initial exposure to an atmosphere of high vinyl chloride concentration a feeling of euphoria sets in, followed by slow reaction time and giddiness (resembling alcohol intoxication); narcosis may follow (42). After leaving this environment, a state of somnolence may persist for one or two days (2, p. 429, and 42, p. 55).

Skin contact with the liquefied gas can produce frostbite (2, p. 427).

Chronic Effects. "Occupational Acroosteolysis" (Vinyl Chloride Disease), is found among workers in the PVC production industry. It is characterized by Reynauds syndrome, hardening of the skin (scleroderma), and lesions of the bone (2, 8, 28, 37). Workers with these symptoms also show clinical symptoms of circulatory disturbances, thrombocytopenia, splenomegaly, and liver changes (42, pp. 6-7).

Radiologic pulmonary changes have been reported in workers exposed to vinyl chloride, and the prevalence of these changes has increased with length of exposure. Exposed workers have also shown a lowering in respiratory volume and vital capacity (42, p. 55) and changes in blood pressure over a 10-year period. Suciu et al. (42, p. 67) found an increase of average systolic pressure of 20 mm Hg and an increase in the diastolic presure of 5 mm Hg.

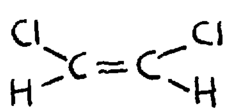
A number of digestive symptoms have been reported by chronically exposed workers, such as anorexia, vomiting, and epigastric pains. In a cohort of Swedish PVC workers, Molina et al., have suggested an increased risk of death from myocardial infarction (40). There is also strong evidence of liver damage in workers chronically exposed to vinyl chloride fumes. Numerous epidemiological studies have demonstrated a significant excess of hepatic cancer (angiosarcoma) among exposed workers (11, 21, 27, 41, 58).

In addition, studies have also suggested that vinyl chloride exposure may be associated with other cancers (respiratory system cancer, brain cancer, lymphomas, and leukemia) (22, 23, 33, 38, 59).

An increase in birth defects (malformations of the central nervous system and genital organs, cleft lip and palate, club foot) has been reported in the offspring of persons in neighborhoods surrounding vinyl chloride polymerization plants. In addition, chromosomal abnormalities and increases in spontaneous abortions among wives of exposed workers have been reported (9, pp. A32-4, 29).

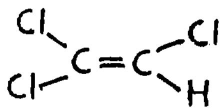
A TLV of 5 ppm has been set for vinyl chloride. NIOSH has recommended an 8-hr TWA of 1 ppm, with a ceiling limit of 5 ppm.

<u>1,2-Dichloroethylene (1,2 Dichloroethene, Acetylene Dichloride)</u>
ClCH=CHCl



1,2-Dichloroethylene is listed as a synfuel.

Trichloroethylene (TCE) (Trichloroethene) $CCl_2{=}CHCl$



Trichloroethylene is a colorless sweet-smelling volatile liquid (35, p. 745) widely used in industry and dry cleaning establishments as a solvent and degreasing agent.

Principal industrial exposures are by inhalation of the vapor. It is readily absorbed into the body through the lungs. It is estimated that 80 to 95% of trichlorethylene used in the U.S. evaporates into the atmosphere (16A).

Another source of exposure is ingestion. Trichloroethylene has been measured in water supplies and in the food chain. Ingested, it readily enters the portal system and is metabolized by the liver.

Acute Effects. Exposures of 1000 ppm may affect visual perception and motor skills. Exposures above 1500 ppm have anesthetic effects and may cause cardiac arrhythmias (2, p. 407). Metabolism of trichloroethylene is enhanced by alcohol, barbiturates, disulfiram, and warfarin causing toxic symptoms at lower exposures (16A, pp. 1-3). Direct skin contact with the liquid solvent can cause irritation, burns, and rashes (16A, pp. 5-19). Exposure to the vapor has been known to cause dermatitis (16A, pp. 5-16).

Chronic Effects. Long-term exposures to levels of 50 to 500 ppm have caused central nervous system symptoms such as dizziness, headache, fatigue, nausea, and fainting spells. Behavioral and psychological effects, especially in the ability to perform menial mental tasks have been reported by some subjects at exposures to 100 ppm and above (6, 7, 55).

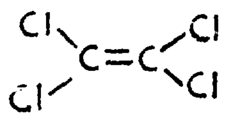
Since the liver and kidney are major target organs of trichlorethylene, liver enlargement, abnormal liver function, fatty liver, and kidney damage have been attributed to chronic increased exposures.

There is some evidence that trichloroethylene is a teratogen and mutagen, but reports are limited to scattered observations in the literature of an increased incidence of miscarriages, stillbirths, and neonatal respiratory and neuromuscular problems among offspring of exposed women. Present available data on mutagenicity and teratogenicity of trichloroethylene are inconclusive (16A, pp. 1-5).

A number of animal studies have shown trichloroethylene to be a renal and liver carcinogen (16A, pp. 1-11), but no direct human evidence has been found.

A TLV of 50 ppm and an STEL of 150 ppm have been set to protect workers against toxic effects (2, p. 407).

<u>Tetrachloroethylene (Tetrachloroethene, Perchloroethylene [Perc])</u>
$Cl_2C=CCl_2$



Perchloroethylene is a colorless moderately volatile nonflammable liquid with an odor like ether. It is a solvent for a variety of organic compounds and is widely used in the dry cleaning industry.

Exposure to perchloroethylene is primarily through inhalation, since it readily evaporates into the atmosphere. It is rapidly taken up by adipose tissue and has an estimated half life of approximateley 70 hours in adipose tissue (18, pp. 5-3). It may take several weeks for perchloroethylene to be completely eliminated from the body.

Acute Effects. Acute exposures, 4000 ppm and above, may be fatal causing central nervous system dysfunction and death through narcosis (35). In controlled human studies, subjects exposed to 100 ppm for up to 7 hours demonstrated depression and behavioral alterations (18, pp. 1-6). As doses increase, central nervous system effects become more marked.

Exposures above 100 ppm have caused eye irritation and sinus congestion (2). Direct contact with liquid perchloroethylene may cause skin burns, blistering, and erythema (2, p. 325).

Chronic Effects. Acute and chronic exposures have the potential of causing liver and kidney damage, since perchloroethylene accumulates in lipid-rich tissue and takes several weeks to be eliminated from the body through the kidneys. Many observers have reported abnormal liver findings in subjects chronically exposed (cirrhosis, toxic hepatitis, liver cell necrosis) (2, 18, 57).

Neurophysiological and psychological changes have been reported in workers chronically exposed (6), as well as other chronic CNS symptoms such as dizziness, headache, nausea, and fatigue (18). Workers have complained of ear, nose, and throat (ENT) irritation from chronic exposure (18, pp. 6-10) and there has been at least one documented case of a young worker with no evidence of heart disease who developed a history of PVCs (Premature Ventricular Contractions) upon exposure to perchloroethylene, which subsided after he was removed from the source of exposure (1).

According to toxicology data bank there have been some scattered reports of workers exposed to perchloroethylene who exhibited a connective tissue disorder similar to vinyl chloride disease, but not enough data were found to substantiate these findings.

Traces of perchloroethylene have been found in breast milk, and Bagnell and Ellenberger cited a case of an infant with an enlarged liver and obstructive jaundice (the mother was exposed to perchloroethylene) whose liver function tests returned to normal after breast feeding was stopped (18, pp. 6-3 and 7-1).

Preliminary studies on yeast cultures have indicated that perchloroethylene might be a mutagen (18, 19, 20, 32), but no conclusive human evidence supporting the mutagenicity of perchloroethylene has been found.

A TLV of 50 ppm has been set to prevent neurological symptoms and eye irritation (2, p. 325).

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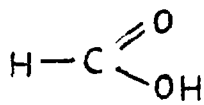
RAC 8	SYSTEM											EFFECT							
VOLATILE ORGANOCHLORINES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Dichloromethane (Methylene Chloride) CH_2Cl_2	X		X		X	X	?	X	X		?				?		X	X	
Trichloromethane (Chloroform) $CHCl_3$	X		X			X	X		X		X	?			?		X	X	
Tetrachloromethane (Carbon Tetrachloride) CCl_4			X			X	X	X	X		X	?					X	X	
1,1,1-Trichloroethane CH_3-CCl_3	X		X		X	X			X			?		?			X	X	
1,1,2-Trichloroethane (Vinyl Trichloride) CH_2Cl-$CHCl_2$			X				?	X	X		?						X	X	
Chloroethene (Vinyl Chloride) CH_2=$CHCl$	X	X	X	X	X	X			X	X	X	X		X	X			X	
Trichloroethylene CCl_2=$CHCl_2$	X		X			X	X		X		X	?	?	?			X	X	
Tetrachloroethylene Cl_2C=CCl_2	?		X	?		X	X	X	X		X		?	?			X	X	

X = known human effect

? = based on animal data, experience with similar compounds, or inconclusive human data

Formic Acid (Methanoic Acid) HCOOH

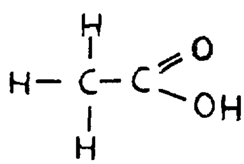


Formic acid is a colorless foul-smelling caustic liquid widely used by the textile and paper industries in dyeing and finishing processes. It is a powerful dehydrating agent and burns readily when ignited.

Its primary effect is as an irritant to mucous membrane. In its liquid form it produces blisters upon contact with the skin and if not immediately washed off will cause ulceration and necrosis. Vapors of formic acid are intensely irritating to the membranes of the eyes, nose, and mouth, and can lead to corrosion of the mouth, throat, and esophagus (4,5,6). Chronic absorption of formic acid has been reported to cause albuminuria and hematuria (3, p. 546; 7).

TLV 2 ppm; STEL 10 ppm (1)

Acetic Acid (Ethanoic Acid) CH_3COOH



Acetic acid is a clear colorless liquid with a pungent odor (1) used in the manufacture of plastics, pharmaceuticals, dyes, insecticides, photographic chemicals, natural latex coagulants, and textile printing. It is also used in the production of acetic anhydride, cellulose acetate and vinyl acetate monomer, acetic esters, and chloroacetic acid (1). Diluted, it is the common household vinegar.

At 10 to 50 ppm the vapors of acetic acid can be irritating to the eye and respiratory tract. At 50 ppm lacrimation, irritation of the eyes, nose, and throat will occur in most persons. If exposures are prolonged, pharyngeal edema and bronchitis may develop. Levels of 800 to 1200 ppm are intolerable after 3 minutes (4). There have been various reports of workers exposed to chronic, long-term levels of 60 to 200 ppm with complaints of chronic conjunctivitis, bronchitis, pharyngitis, tooth erosion, various abdominal complaints, (digestive disturbances and constipation), and skin irritations (1, 2, 7).

In the liquid form, acetic acid is strongly corrosive to the skin, eye, nose, and mouth. Its action is insidious since there is no immediate burning sensation and blistering may take 30 minutes to 4 hours to develop. Workers have reported cracking and dryness of the palms of their hands in working with acetic acid, and blackening and hyperkeratosis of the skin has been reported with chronic exposures (5, 6).

Ingested, glacial acetic acid can perforate the esophagus.

TLV 10 ppm; STEL 15 ppm (1).

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RAC 9	SYSTEM											EFFECT							
VOLATILE CARBOXYLIC ACIDS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Formic Acid HCOOH			X			X	X	X									X		
Acetic Acid CH_3COOH		X	X			X		X									X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #10 - VOLATILE O AND S HETEROCYCLICS

Listed in RAC #10, volatile O and S heterocyclics are derived from a five-membered heterocycle ring with either an oxygen or sulfur atom as a member of an aromatic ring.

Oxygen Heterocyclics

<u>Furan</u> (1,4-Epoxy-1,3-Butadiene; Furfuran) C_4H_4O

Furan is a colorless highly flammable liquid, with a strong ethereal odor. It occurs in oils obtained by the distillation of pine wood resin. Furan is utilized in the production of other industrial chemicals (pharmaceuticals, herbicides, stabilizers, and fine chemicals).

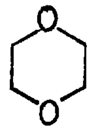
Furan is a highly volatile liquid. Since it can be absorbed through skin, direct contact should be avoided. It is a constituent of tobacco smoke, and its toxicity (and metabolism) in the lung has recently attracted more attention in research (2). No record of injury due to occupational exposures to furan has been found (3).

<u>Tetrahydrofuran</u> (THF, 1,4-Epoxybutane, Diethylene Oxide, Tetramethylene Oxide) C_4H_8O.

THF is a colorless liquid with an ethereal odor. It is a solvent for natural and synthetic resins, particularly vinyls. It is also a chemical intermediate and monomer.

Experiments with animals show skin irritation, increased pulse rate, and evidence of kidney damage in cats and rabbits after exposures of 3,400 to 17,000 ppm (1, 4). No documentation of human data was found.

Dioxane (1,4-Diethylene Dioxide) $O(CH_2CH_2)_2O$



Dioxane is a colorless flammable liquid, with an ethereal odor. It is used as a solvent for a wide range of organic products. A major use has been as a stabilizer in chlorinated solvents.

Animals studies show the toxicity of dioxane, particularly if it is introduced intraperitoneally. Nasal and liver tumors were reported in rats ingesting 7,000 to 18,000 ppm of dioxane in drinking water for 14 to 23 months.

Human studies are relatively scarce. There are reports of five workers in an artificial silk factory who died of kidney damage and liver necrosis after approximately two months' exposure to dioxane. Other workers suffered from nausea, vomiting, and irritation of eyes and respiratory passages. Death has been reported in a worker after one week on a job where the average concentration of dioxane vapor was 470 ppm. There was a possibility of skin absorption. Damage to the kidneys, liver, and brain were seen on autopsy. ther workers similarly exposed were unaffected. Studies on other plants with average vapor concentrations 1.07, 0.9, and 6.5 ppm, and the corresponding maximum values 7.2, 2.0, and 23.6 ppm, respectively, showed lack of unusual cancer incidence or mortality. In one of these studies, both liver and kidney functions tests were abnormally high for a few workers (1).

There is a controversy as to the recommended standard of dioxane. NIOSH (1976) suggested 1 ppm and ACGIH (1) suggested 25 ppm.

Sulfur Heterocyclics

Thiophene (Thiophuran; Thiofurfuran; Thiotetrole; Diuinylene Sulfide) C_4H_4S

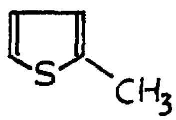
Thiophene is a liquid with slight aromatic odor resembling that of benzene. It is found in coal tar, in coal gas, and in technical benzene. It is used in the manufacture of resins, dyes, and pharmaceuticals.

Thiophene is dangerous when heated to decomposition since it emits highly toxic fumes of sulfur oxides (4).

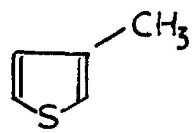
No human data on exposure to thiophene have been found.

Methyl Thiophene $C_4H_3CH_3S$

2-Methyl thiophene (α-thiophene)



3-Methyl thiophene (β-thiophene)



No human data on methyl thiophenes have been found.

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RAC 10	SYSTEM											EFFECT							
VOLATILE O & S HETEROCYCLICS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Furan C_4H_4O		X	X														X		
Tetrahydrofuran C_4H_8O		No human data found																	
Dioxane $O(CH_2CH_2)_2O$						X	X	X	X		X	?							
Thiophene C_4H_4S		No human data found																	
Methyl Thiophene $C_4H_3CH_3S$		No human data found																	

X = known human effect

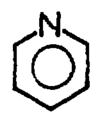
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #11 - VOLATILE N HETEROCYCLICS

Nitrogen heterocyclics contain nitrogen as a member of an aromatic or aliphatic carbon ring. RAC #11 includes 1) aromatic N heterocyclics (piridine and three isomers of methyl piridine), and 2) aliphatic N heterocyclics (ethylenimine, pyrrolidine, and piperidine).

Aromatic N Heterocyclics

<u>Pyridine</u> C_5H_5N



Pyridine is a flammable colorless iquid with a disagreeable odor detectable below 1.0 ppm. It is used to denature alcohol and as a solvent in the paint and rubber industries. It is also used in the manufacture of pharmaceuticals, dyes, pesticides, polycarbonate resins, and water-repellent finishes fo: textiles.

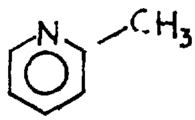
Ingested, pyridine affects the central nervous system. Smaller doses stimulate bone marrow to increase production of blood platelets. Large doses act as a heart poison. The dose 0.83 to 2.46 ml of pyridine used for treatment of epilepsy appeared to be toxic, with one death from liver and kidney damage. The vapor of pyridine affects mucous membrane causing nasal and eye irritation. Inhalation causes chronic poisoning centering in the liver, kidney, and bone marrow (1, 10).

Exposures of 6 to 12 ppm produced chronic poisoning with mild symptoms of central nervous system injury. Transient symptoms of overexposure are nausea, headache, insomnia, nervousness, mental depression, and low back or abdominal discomfort with urinary frequency. These symptoms have been reported in workers exposed at levels from 15 to 330 ppm (1, 2, 6, 7, 9).

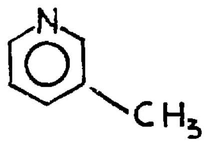
Prolonged or repeated skin contact causes irritation.

Reports of injurious effects of pyridine are rare despite its widespread industrial use.

Methyl Pyridines (Picolines) $C_5H_4CH_3N$



2-methyl pyridine (α-picoline)



3-methyl pyridine (β-picoline)

4-methyl pyridine (γ-picoline)

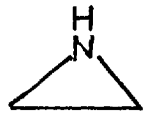
Methyl pyridines are colorless liquids with strong odors. They are found in coal tar and in bone oil. 2- and 3-methyl pyridines are used as intermediates in dye and resin industries; 4-methyl pyridine is used in the manufacture of isonicotinic acid and derivatives, and in waterproofing agents for fabrics.

Clinical signs of intoxication used by 2- and 3-methyl pyridines include weight loss, diarrhea, weakness, ataxia, and unconsciousness (8, 10).

Studies on mutagenic activity of aromatic nitrogen compounds indicate that the alkylation of pyridine did not produce a mutagen (3).

Aliphatic N Heterocyclics

Ethylenimine (Ethylene imine, Aziridine, Azacyclopropane, Dimethylenimine) $(CH_2)_2NH$



Ethylenimine is a clear extremely flammable caustic liquid with an intense odor of ammonia. It is used in a variety of industrial applications (usually as a polymer) such as paper and textile chemicals; adhesives; binders; petroleum refining chemicals, fuels, and lubricants; coating resins; varnishes; lacquers; agricultural, cosmetic, and photographic chemicals; etc.

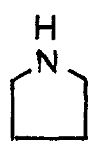
Ethylenimine is highly toxic by skin contact, ingestion, and inhalation. Direct contact may cause eye and skin irritation, and a slowly healing dermatitis (1). The vapors may cause severe irritation of the eyes and throat, and produce inflammation of the respiratory tract, lung edema and hemorrhage, and kidney damage. A decrease in white blood cell count and depression of all formed blood elements have been observed, and thus polyaziridine has been used as a cancer chemotherapeutic agent (1, 4, 6).

Numerous experiments on animals indicate carcinogenic activity of ethylenimine. The mutagenic activity in lower organisms (Drosophila, Neurospora, Saccharomyces) has been recognized (1, 6).

In spite of the serious nature of animal findings, industrial experience has been good. An epidemiologic study of 144 ethylenimine workers, some of whom had 40 years' experience, revealed no evidence of an increased risk of cancer among these workers (1).

FDA and OSHA list ethylenemine as a carcinogen (4, 5).

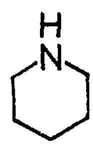
Pyrrolidine (Tetrahydropyrrole) C_4H_8NH



Pyrrolidine is an almost colorless liquid with an unpleasant ammonia-like odor. It is found in tobacco and carrot leaves. It is one of predominant amines found in tobacco and cigarette smoke condensate (10). Carcinogen N-nitrosopyrrolidine is formed in fried bacon from proline via pyrrolidine (10).

Pyrrolidine, a strong base, is an irritant to skin and mucous membranes. When heated to decomposition, it emits highly toxic fumes of NO_2.

Piperidine (hexahydropyridine) $C_5H_{10}NH$



Piperidine is a highly irritating liquid with a characteristic odor. It may cause death or permanent injury after very short exposure to small amounts.

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10. Toxicology Data Bank, National Library of Medicine. (Computer search 1982).

RAC 11	SYSTEM											EFFECT							
VOLATILE N HETEROCYCLICS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Pyridine C_5H_5N	X		X		X	X	X	X	X		X						X		
Methyl Pyridine $C_5H_4CH_3N$						X			X										
Ethylenimine $(CH_2)_2NH$		X	X		X		X	X				?		?			X		
Pyrrolidine C_4H_8NH			X					X									X		
Piperidine $C_5H_{10}NH$								X									X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

Benzene (Benzol, Phene) C_6H_6

Benzene is a colorless volatile liquid aromatic hydrocarbon with a specific odor. Ninety-four percent is produced by distillation of petroleum and 6% by the coking process in steel mills.

Benzene is used in the synthesis of polymers, detergents, and pesticides, as an intermediate in clinical and pharmaceutical industries; in the preparation of chloronitrate solvents; in the rubber industry; in cements and adhesives; as components of inks in printing; in thinners; and as a degreasing and cleaning agent. Benzene has been added to gasoline (2% in USA, 4 to 5% in Europe) to replace lead tetraethyl. It is ubiquitous in the workplace, and with its vapor pressure of 74.6 mm Hg at 20°C, it easily escapes into the environment. The present U.S. standards for occupational exposure during an 8-hr day, 40-hr week time weighted average (TWA) is 10 ppm (32 mg/m^3) with a ceiling value (15 min) of 25 ppm and an allowable peak value of 50 ppm (1).

The ambient benzene in air varies from 0.1 to 14 ppb. Dietary intake may be as high as 250 µg/day.

Toxicity. Toxic effects of benzene have been known since the turn of the century. Inhaled benzene is absorbed rapidly in the lung. The benzene concentration in blood reaches about 70% of the air content in 30 minutes. About 40% of inhaled benzene is exhaled unchanged. Since it is highly soluble in lipids, it accumulates in fat-containing organs. The highest levels are found in bone marrow, fat, and nervous tissues. Complex metabolic pathways of benzene include formation of benzene oxide, phenol, hydrozinol, and catechol which are biologically active and may account for a large part of its toxicity (1, 7, 14, 15, 17).

Phenol excreted in urine is the end product of benzene metabolism. The methods evaluating the exposure to benzene and its distinction from the exposure to other organic solvents (toluene, xylene, styrene, etc.) are based on the analysis of urinary samples (4, 6). The measurement of phenol/creatinine ratio in urine is considered a highly sensitive method to evaluate the atmospheric concentration of benzene (14A). Increased concentration of phenol in urine occurs parallel to the decrease of thrombocytes and leucocytes in blood (11, 12).

Acute Toxicity. The primary acute toxic effect of benzene is on the central nervous system and is seen initially at exposures above 250 ppm. Exposure to massive concentrations, around 2.5% by volume in air (about 25,000 ppm) is fatal within minutes. The prominent signs are central nervous system depression and convulsions, with death usually following as a consequence of cardiovascular collapse.

Fatalities have occurred after benzene inhalation in closed spaces such as tanks. Severe nonfatal cases exhibit similar signs, but recovery occurs after a period of unconsciousness. Milder exposures (4000 ppm) produce euphoria followed by giddiness, headache, nausea, staggering gait, and finally unconsciousness if exposure continues. Inhalation of lower concentrations (250 to 500 ppm) produces vertigo, drowsiness, headache and nausea, symptoms which clear rapidly once exposure ceases. Deaths from cardiac sensitization and cardiac arrhythmias have also been reported after benzene exposure to unknown concentrations (1, 7, 15A, 17).

Exposures above 50 ppm for extended periods may produce changes in the bone marrow, which result in decreased levels of platelets, red blood cells, or white blood cells (pancytopenia). Benzene-induced pancytopenia is characterized by a relatively frequent occurrence of bone marrow hyperplasia. A milder form, unicytopenia, includes cases of anemia, granulocytopenia, or thrombocytopenia. In its most severe form, damage to the bone marrow results in aplastic anemia. About 13% of these cases of benzene-induced aplastic anemia are fatal. The signs of chronic benzene poisoning can appear any time following a few weeks to several years of exposure. Typical symptoms are rather nonspecific: severe fatigue, headache, dizziness, nausea, vertigo, stomach pain, loss of appetite, or feeling cold (7, 13, 17, 18, 20). Neurological abnormalities were reported in four out of six pancytopenic patients with chronic benzene poisoning (3, 5).

Prolonged or repeated skin contact may produce a dry, scaly dermatitis, erythema, and blistering.

Carcinogenic Effects - Leukemia. While aplastic anemia is a major complication of benzene toxicity, acute leukemias of the marrow-formed blood elements are the most severe manifestations of benzene toxicity.

The evidence for benzene-induced leukemia is largely from epidemiological studies (7, 18, 20). Increased incidence of leukemia was observed in some industries (shoemakers, certain rubber products, etc.) where benzene in high concentration mixed with other solvents was handled indoors and in unventilated areas (2, 3, 13A). In all well-documented cases of benzene-related leukemia, victims developed a previously detectable decrease in blood levels of one or more of the cell lines.

The implications of these observations for the relationship between benzene exposure and leukemia are twofold: 1) chronic exposure to high concentrations of benzene appear to be required, and 2) decreases in blood concentrations of platelets, leukocytes, and/or red blood cells may be an important early warning of leukemia risk in workers exposed to benzene (13, 14).

Cellular Mechanism. The mechanism by which benzene produces its hematologic and carcinogenic effects in humans is still unknown. Commonly observed chromosomal abnormalities in occupationally exposed individuals, in experimental animals, and in human cells cultured *in vitro* suggest an effect on the function of stem cell nuclei (13, 15B, 15). Pancytopenia may represent either a destruction of bone marrow stem cells, a failure of these cells to differentiate, or a destruction of more mature precursors of hematopoietic cells. Muconaldehyde has been recognized as a potential toxic intermediate of benzene metabolism. When incubated with human peripheral blood cultures, muconaldehyde inhibited erythroid stem cell production (13). Macrocytosis represents the most frequently reported abnormality of red cells. Evidence of decreased platelet function was also demonstrated in numerous investigations (7, 13, 20).

Experimental exposure of cultured human lymphocytes to different toxic compounds showed that benzene inhibited [3H] thymidine uptake in the absence of NADH-generating system (S9 mix) but had no effect on cell viability. These observations suggest that a cytotoxic action of benzene is not immediately followed by cellular death (16).

Goldstein (13) points out that the evidence of altered lymphocytic function in humans is indirect, consisting mainly of studies suggesting aberrant immune function. An effect of benzene on lymphocytes implies that the target of benzene hematotoxicity is not simply the myeloproliferative stem cell. It raises the possibility that benzene leukemogenesis is a result of altered immune function. Such supposition is based on the current theoretical concept of the role of immune surveillance in carcinogenesis. Further studies are indicated in order to evaluate the role of lymphocytes in benzene hematotoxicity, to establish whether the effect is specific for B or T lymphocytes, and to evaluate the possible interaction of benzene with supressor lymphocytes (13, 17). Casale (8) suggested that the aplastic anemia may represent a stem-cell defect, a hostile microenvironment, or an autoimmune phenomenon; immunosuppression and bone marrow transplantation are considered as particularly promising therapies. Increased formation of immunoglobin and alterations in lymphocyte nuclei have been recognized as early signs of an enhanced immune reactivity following chronic exposure to benzene (9). Flow cytofluorometry has also been applied for the evaluation of early proliferative change in bone marrow from persons exposed to benzene (13A).

Incidence. The literature reporting benzene hematotoxicity includes single-case reports and series of case reports of individuals with a relatively unique benzene exposure experience. Since the mild symptoms are often not reported by the patient, or not associated with the exposure to benzene, the total incidence of benzene-induced pancytopenia is unknown (20). There are very few studies of the longitudinal assessment of groups of workers previously exposed to benzene. The long-term study which evaluated 147 persons exposed to benzene in a shoe factory showed that 107 persons had abnormal blood count. Nine years after cessation of the exposure to benzene, 125 of these workers were reexamined. The mean leucocyte count was improved; however, the mean erythrocyte and platelet counts remained significantly less than the control level (13). A follow-up study lasting 18 years reported 10 deaths within a cohort of 60 workers occupationally exposed to benzene. Four deaths were due to malignancies, but no leukemia was observed. Workers with slight initial hematologic disorders related to benzene exposure returned to normal (13B). In a chemical plant where benzene was used in large quantities, a cohort of 259 males employed at any time between 1947 and 1960 was followed through December 31, 1977. Fifty-eight deaths were identified, four resulting from lymphoreticular cancers, when 1.1 would have been expected. Three of the deaths were due to leukemia and one was caused by multiple myeloma. In addition, one of the leukemias had multiple myeloma listed on the death certificate. These findings raise the possibility that besides leukemia, multiple myeloma could also be linked to benzene exposure (10). Additional follow-up studies of large groups of benzene-exposed individuals are indicated (13).

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RAG 12	SYSTEM											EFFECT							
BENZENE	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Benzene C_6H_6	X		X		X	X			X			X					X	X	

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #13 - ALIPHATIC/ALICYCLIC HYDROCARBONS

Aliphatic hydrocarbons discussed in RAC #13 include: (alkanes) ($C_nH_{(2n+2)}$) with straight carbon chains: (a) C_5 to C_8; (b) C_9 to C_{12}; and (c) their isomers.

Alicyclic hydrocarbons are represented by methylcyclopentane.

Alkanes With C_5 to C_8 Carbon Chains (pentane, hexane, heptane, and octane)

Alkanes are colorless liquids with a light petroleum odor, produced almost exclusively from petroleum. They are used in a variety of industrial applications: as solvents in glues, in varnishes, in the extraction of oils from various seeds, and in the formulation of gasoline.

Commercial alkanes contain mixtures of hydrocarbons. Analysis of commercial pentane showed 76% n-pentane, 21% isopentane, and small quantities of butane and hexane. Commercial hexane is mostly a mixture of hexane isomers with roughly one third n-hexane, and small amounts of cyclopentane and cyclohexane, and of pentane and heptane isomers. Commercial heptane is largely composed of isomers of heptane (1, 7, 24).

Since exposure of workers to only one alkane is infrequent, NIOSH has recommended TWA concentration 350 mg/m^3 as the occupational limit for pentane, hexane, heptane, octane, and total alkanes (mixture) (14).

Generally alkanes from pentane (C_5) through octane (C_8) show increasingly strong narcotic properties. Early symptoms of exposure to alkane vapors include headache, burning sensation on the face, abdominal cramps, and vertigo. The physiologic response in humans to alkanes increases markedly with increasing numbers of carbon atoms (7, 14, 23).

Similarly, the alkane concentrations required to produce a physiologic response decreases as the number of carbon atoms in the compound increases. A 10-min exposure to pentane at 5000 ppm or to hexane at 2000 ppm caused no symptoms of intoxication, but a 10-min exposure to hexane at 5000 ppm caused marked vertigo. Heptane caused moderate vertigo after 4-min exposures at 3500 ppm, and marked vertigo after 4-min exposures at 5000 ppm (5, 7).

Several reports show that exposure of workers to n-hexane causes polyneuropathy and polyneuritis (1, 20, 21). In most cases, however, no measurements of solvent vapor concentration was reported. Sax suggested that occupational neuropathy resulted from exposures as low as 500 ppm and below (21). Recently Iida (10) reported outbreaks of polyneuropathy and neurotoxicity in sandal factory workers exposed to 50 ppm of n-hexane. The need for lowering the TLV level for n-hexane and cyclohexane in shoe factories was suggested by Mutti et al. (12, 13) who also considered the possibility of the synergistic effects of the two hydrocarbon solvents. Potentiation of hexacarbon neurotoxicity by methyl-ethyl-ketone has been recognized in other studies (1A, 11). The evidence seems fairly convincing that the neurotoxic effect of n-hexane is not possessed by other hexane isomers; however, other alkanes, especially heptane, may also be neurotoxic (4).

There have been some recent studies on the neurotoxicity and metabolism of hexane. The recognition that 2,5-hexanedione was the principal n-hexane metabolite found in the urine of shoe-factory workers exposed to commercial hexane was consistent with the idea that this compound was responsible for the development of neuropathy (17-19). In experimental conditions 2,5-hexanedione and other gamma-diketones reacted with primary amines forming pyrrole adducts (6). These authors suggested that the pyrrole formation is the probable mode of in vivo tissue binding of 2,5-hexanedione.

Clinical and morphological studies of cases of neuropathy due to n-hexane reveal alterations of both myelin sheaths and axons (22). Study of H-reflex behavior in n-hexane neuropathy gives evidence of spinal involvement in these patients (2); others also suggest the neurotoxic effect of n-hexane on the central nervous system (13). Studies on the respiratory uptake and elimination of n-hexane during physical exercise show considerable differences in inspired hexane at different levels of exercise (25). Although the exact mechanism of hexacarbon neurotoxicity has not yet been identified, an interference with neuronal axoplasmic flow seems most likely.

No studies correlating environmental concentrations of pentane, hexane, heptane, with observed toxic effects have been found, except for those relating industrial exposures to n-hexane with the development of polyneuropathy. Nor were any long-term epidemiologic studies of low-level occupational exposures to alkanes found.

Octane has been reported as a compound producing giddiness, vertigo, headache, and anesthetic stupor or apneic anoxia. Also, epileptiform seizures were observed months after acute episodes. Pathological examination of tissue from fatal cases showed widespread microhemorrhage (23).

Effects of liquid alkanes on the skin were studied on five volunteers under laboratory conditions. One-hour skin contact produced irritation, and swelling. Blisters appeared after longer exposure (16, 20, 21). Increased numbers of carbons in the alkane chain were correlated with the increased intensity of symptoms and with the increased length of time needed for the disappearance of pain after removal of alkanes (8).

Morphea-like skin lesions have been recognized in patients with systemic scleroderma who were engaged in occupations exposing them to organic solvents for a long time before the symptoms appeared (26).

No studies showing carcinogenic, mutagenic, or teratogenic potential of alkanes (C_5-C_8) have been found.

Alkanes With C_9 to C_{12} Carbon Chains (nonane, decane, undecane, and dodecane)

Nonane and decane in high concentrations are central nervous system depressants. They are considered relatively nontoxic. The 5-nonanone showed the same degree of neurotoxicity as n-hexane and methyl-n-butyl-ketone. The neurotoxicities of these three compounds were limited by virtue of their metabolism to a gamma-diketone (15). No epidemiological studies on the effects of C_9-C_{12} alkanes have been found.

Undecane and dodecane. No human data were found. Animal studies suggest that dodecane may act as a potentiator of the skin carcinogen benzo[a]pyrene.

Hexane Isomers C_6H_{14}

2-Methylpentane. The toxic effect has not been sufficiently investigated, although irritation of mucous membranes and a low oral toxicity are suspected. There is no evidence of neurotoxicity (16, 23).

3-Methylpentane. The toxicity is presumably parallel to that of 2-methylpentane, but no data on human reaction have been found.

2,2-Dimethylbutane. No data found.

2,3-Dimethylbutane has been found in glue solvents which cause polyneuropathy; there are, however, no data indicating what component of the solvent was the causative agent.

Alicyclic Hydrocarbons

Methylcyclopentane (Methylpentamethylene) C_6H_{12}. Methylcyclopentane was a component of glue solvents which produced polyneuropathy, but the effects of separate components of glue solvent have not been determined.

The concentration of n-hexane and its isomers, acetone, and methylcyclopentane, was measured in the environmental air in a shoe factory and in the alveolar air and blood of workers. Lung uptake and alveolar and blood concentration were correlated with environmental concentration of methylcyclopentane, 2-methylpentane, and 3-methlypentane (3).

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RAC 13	SYSTEM											EFFECT							
ALIPHATIC/ALICYCLIC HYDROCARBONS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Alkanes with C_5-C_8 carbon chains			X			X			X									X	
Alkanes with C_9-C_{12} carbon chains								X	X								X	X	
Alicyclic Hydrocarbons									X										

X = known human effect

? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #14 - MONO/DIAROMATIC HYDROCARBONS (EXCLUDING BENZENE)

Mono- and diaromatic hydrocarbons are derivatives of benzene.

Monoaromatic Hydrocarbons

Monoaromatic hydrocarbons are single ring aromatic hydrocarbons with one or more substitutions.

Alkyl Benzenes (toluene, xylene, ethyl benzene, cumene, styrene, and methyl styrene) are single benzene ring compounds, with aliphatic side chains attached. They are colorless liquids with a relatively low boiling point and a characteristic odor of aromatic hydrocarbons. Human exposure to concentrations up to 200 ppm produce mild to moderate symptoms of fatigue, headache, and eye and throat irritation. Concentrations above 200 ppm produce gastrointestinal symptoms, injuries to the heart, liver, and kidneys, pulmonary injuries, and neurological disturbances. Concentrations reaching about 800 ppm and/or long-term exposures may be fatal.

Indene and indan are single benzene ring compounds with a cyclopentane ring attached. The toxic effects of indene and indan have not been studied in humans. Experiments on animals suggest possible inhalation toxicity.

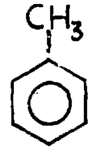
Diaromatic Hydrocarbons

Diaromatic hydrocarbons include hydrocarbons composed of two benzene rings (biphenyl, naphthalene) and their methyl-derivatives (methyl naphthalenes). Diaromatic hydrocarbons appear as crystalline halves or scales with strong specified odor. Exposure to the fumes affects the gastrointestinal, pulmonary, and nervous systems. Severe intoxication may be produced by ingestion.

Monoaromatic Hydrocarbons

Alkyl Benzenes

Toluene (Methyl Benzene, Phenyl Methane, Toluol) $C_6H_5CH_3$. Toluene is a clear liquid with benzene-like odor. The major source (96%) is from petroleum. About 70% of produced toluene is converted into benzene. Another 15% is used in the production of chemicals, and the remainder is used as a solvent for paints and as a component of gasoline.



Exposure to toluene produces neurotoxic effects. Experimental 8-hr exposures to essentially pure toluene at concentrations up to 200 ppm produced mild to moderate fatigue, slight headache, and mild eye and throat irritation. Increased concentrations of toluene up to 400 ppm intensified the above symptoms and produced muscular weakness, impaired coordination, and moderate dilation of pupils. Exposures at 400 to 800 ppm produced narcotic effects leading to mental confusion, considerable incoordination, lack of self-control, and staggering gait. Similar effects were observed in 100 workers exposed to toluene concentrations ranging from 50 to 200 ppm, 200 to 500 ppm, and 500 to 1500 ppm (1, 40, 42, 52, 59). An increased risk of neuropsychiatric diseases has been recently reported in epidemiological studies in Finland (29A).

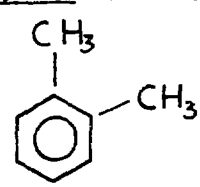
Most reports of occupational exposures to toluene lack information about either the purity of toluene or the accurate atmospheric concentration of toluene and other solvent vapors at work sites (1).

Acute low-level exposure to organic solvent vapors may result in prenarcotic states of central nervous system depression. Progressive increase of reaction time was observed at toluene exposures of 300 ppm/30 minutes (65).

Inhalation of high doses (glue sniffing) produces encephalopathy and may lead to permanent neurological damage (7), cerebellar degeneration (29), cerebral cortical atrophy (53), optic neuropathy and the loss of hearing (15), or sudden death from cardiac arrhythmia (1). Clinical findings on 25 adults hospitalized for problems related to paint sniffing showed neuropsychiatric disorders (altered mental status, cerebellar abnormalities, and peripheral neuropathy) in 10 patients, muscle weakness in 9 patients, and gastrointestinal complaints in 6 patients. Laboratory data showed a decrease in potassium and phosphorus and an increase in chlorine and carbon dioxide in the blood serum (55). Renal acidosis and multiple metabolic abnormalities were recognized in a group of 16 patients hospitalized for paint sniffing (62). Hypokalemic periodic paralysis was also reported in dermic exposure to toluene (8). Toluene skin contact can cause irritation.

Reports on the effects of toluene on the hematopoietic system are not clear since the benzene content of the toluene was not reported. Some studies on chromosome aberrations report that the exposure to toluene does not affect sister chromatid exchange (23, 30). However, cytogenetic analyses of peripheral leucocytes from 20 male workers exposed only to toluene for more than 16 years showed yields of chromatid breaks, chromatid exchanges and gaps significantly higher than in a group of 24 unexposed workers (7). Cytoenzymatic studies of neutrophils in workers show that the exposure to solvents containing benzene, toluene, and xylene produces increased activity of acid phosphatase and beta-glucuronidase, decreased activity of peroxidase and decrease in glycogen reserves (32, 33). Metabolic end product toluene is hippuric acid excreted in the urine. The correlation between exposure to toluene and excreted hippuric acid is commonly observed (2, 4, 22, 28, 31, 57, 58, 60, 61). However, the intake of benzoic acid in foodstuffs (raisins, coffee, certain fruits and vegetables, preservatives, and medicine) can cause a 3-fold increase in the excretion of hippuric acid and in particular cases a 10-fold increase in the normal excretion (64, 66). Thus the food intake should be considered in the evaluation of toluene exposure when measuring hippuric acid excretion. A number of studies are devoted to the improvement of laboratory methods evaluating the excretion of hippuric acid (9, 11, 25, 34, 36-39, 43, 47, 56).

Xylene (Dimethyl Benzene, Xylol) $C_6H_4(CH_3)_2$



Xylene is a clear flammable liquid with an aromatic hydrocarbon odor. Commercially available xylene is a mixture of three isomers (ortho, meta, and para). Xylene is used extensively as a solvent in paints. All isomers are used in making drugs, dyes, and insecticides, and in the preparation of phthalic acids. Xylene is also present in gasoline.

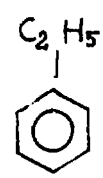
Toxic effects of xylene are similar to or higher than toluene. Workers exposed to xylene complained of headache, fatigue, lassitude, irritability, and gastrointestinal disturbances. Neurological disturbances, and injury to the heart, liver, kidneys, and nervous system were also observed. Xylene and toluene are probably greater irritants than benzene to the eyes and mucous membranes of the respiratory tract (1). Epileptiform seizures were reported in a patient after a brief exposure to xylene vapor and in a patient who had sniffed glue (1, 5, 27). The death from aplastic anemia of a lithographer who used xylene for several years has also been reported (1). In most cases of blood disease associated with xylene, the presence of benzene as an impurity was not ruled out.

The product of xylene metabolism is methylhippuric acid excreted in urine. Its distinction from the urinary hippuric acid by new methods allows the evaluation of xylene and toluene exposures (37-39). Controversial results were reported on the effect of xylene and alcohol on the central nervous system. Xylene either enhanced (48, 49) or counteracted (54) the effect of alcohol. In one study, ingestion of ethanol before exposure to xylene produced an 1.5- to 2.0-fold increase in the blood xylene level and about a 50% decline in the excretion of urinary methylhippuric acid, thus suggesting that ethanol decreased the metabolic clearance of xylene (46).

Acute impairment of body balance directly related to the xylene uptake was correlated with xylene concentration in the blood. Riihimaki (46) considers that brain tissue will reach xylene equilibrium within a few minutes and brain xylene concentration probably closely follows blood xylene levels. Inhalation exposure of male volunteers to m-xylene (200 pm) for 4 hours at 6-day intervals over a six-week period induced only slight changes in psychophysiological functions (body sway and reaction time) (48-51). Postexposure excretion of xylene from most tissues except adipose tissue takes place rapidly. The uptake of xylene by adipose tissue is greatly enhanced by physical exercise (17, 45).

Xylene has a defatting action on the skin and contact can cause erythema and blistering (19A).

<u>Ethyl Benzene</u> $C_6H_5C_2H_5$



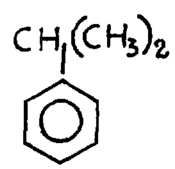
Ethyl benzene is a colorless, flammable liquid with an aromatic odor. It is used as a solvent and as an intermediate in the production of styrene.

Ethyl benzene toxicity produces skin and less markedly mucous membrane irritation. Skin reddening, exfoliation, and blistering observed in rats suggested that ethyl benzene is the most severe irritant of the benzene series.

Human exposure to 200 ppm produces transient eye irritation. Increased concentration up to 2000 ppm produces immediate and severe eye irritation and lacrimation accompanied by moderate nasal irritation. Vapor concentrations at 5000 ppm cause intolerable irritation (1).

Aspiration of a small amount of ethyl benzene can cause severe pulmonary injury. TDB reported the possiblity of toxic hepatitis, leukopenia, and lymphocytosis from prolonged exposure. The acute toxicity is low (10,000 ppm is fatal for guinea pigs in a few minutes). Studies on simultaneous exposures to ethylbenzene and xylenes indicate a competitive reaction mechanism between these compounds and suggest possible carcinogenic properties of epoxides formed as intermediates (4).

<u>Cumene (Isopropylbenzene, 2-Phenylpropane, 1-Methyl Ethyl Benzene)</u>
$C_6H_5CH(CH_3)_2$

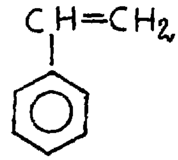


Cumene is a colorless liquid manufactured exclusively from propylene and benzene. It is used in the production of acetone, phenol, and methylstyrene, and as a solvent.

Cumene is a potent narcotic but the hazards of use are minimized by virtue of its relatively high boiling point and hence low vapor pressure. Cumene is considered a primary skin and eye irritant. It is absorbed by the skin more rapidly than toluene, xylene, or ethylbenzene. The small quantity of cumene absorbed in blood is exhaled unchanged, but the major portion is metabolized in the liver and excreted in the urine as conjugated alcohols or acids (1).

The suggested TLV of 50 ppm and STEL of 75 ppm are recommended on the basis solely of animal studies. East Germany and USSR recommendations (1972/73) are 10 ppm.

Styrene (Phenyl Ethylene, Ethenylbenzene, Vinyl Benzene) $C_6H_5CH{=}CH_2$



Styrene monomer is a colorless oily liquid with an aromatic odor. It is commonly used in making polystyrene plastics, protective coatings, styrenated polyesters, copolymer resins, as a solvent, and as a chemical intermediate.

"Styrene sickness" (lightheadedness, drowsiness, nausea, and dizziness) has been reported after exposures at 200 to 700 ppm (1).

The accumulation of acute toxic quantities is unlikely since odor threshold is 0.1 mg/liter, and is objectionable at 200 ppm. Increased accumulations produce neurological impairment and strong irritation of eyes and nasal mucous membrane. Concentrations of 800 ppm produce immediate eye and throat irritations, nasal mucous secretion, drowsiness, and vertigo. After three hours' exposure, slight muscular weakness occurs accompanied by inertia and depression (40).

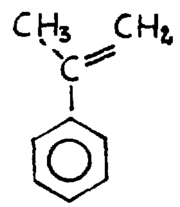
Metabolic end products of styrene are phenylglyoxylic acid and mandelic acid which are excreted in urine. The measurements of these acids in urine serves as biological monitors for the evaluation of exposure to styrene (10, 13, 14, 16, 18, 19, 21, 64). The metabolites are rapidly removed from the body after cessation of exposure (44, 67).

ACGIH quotes a study by Dutkiewicz and Tyras which found that a brief contact of the hands with styrene, or one hour contact with styrene-saturated water resulted in absorption as great as 8 hours' inhalation of 12 ppm. However, mandelic acid excretion was much less than after lung absorption.

Styrene has been observed to cross the placental barrier and to produce defects in the central nervous system of offspring, although it is not clear if other solvents were involved. Reported chromosomal alterations are controversial. Andersson et al. (3), and Watanabe et al. (63) concluded that chromosome aberrations are not correlated with exposure to styrene. A distinct dose-dependent increase in sister-chromatid exchanges has been found in human whole-blood lymphocyte cultures treated with styrene, its methyl substituted derivatives, and with styrene oxides (35). The authors conclude that styrene and methyl styrenes were apparently converted into reactive metabolites in the above culture.

Lymphocytes from 38 individuals occupationally exposed to styrene (1-40 ppm) showed a significant increase in the mean level of N-acetoxy-2-acetylaminofluorene-induced unscheduled DNA synthesis (UDS) but no significant effect of UV-induced UDS (41). Lymphocyte cultures *in vitro* exposed to styrene (100 mM) in the same study confirmed the above findings. The authors conclude that styrene exposure apparently does not inhibit DNA repair synthesis, but rather it predisposes lymphocytes to an increased risk for DNA damage induction from subsequent genotoxic exposures. Anemia and morphofunctional alterations of erythrocytes were reported by Gribova et al. (20) and by Khristevaand Mirchev (26).

α-Methyl Styrene (2-Phenyl Propene) $C_6H_5C(CH_3) = CH_2$

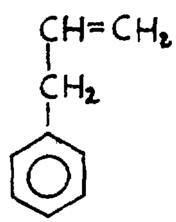


α-Methyl styrene is a polymerizable liquid monomer.

Human subjects exposed to a concentration 200 ppm of α-methyl styrene reported definite unpleasant odor and slight eye irritation after two minutes of exposure. No adverse effect was found in animal studies (40, 42).

Severe or prolonged exposure may cause depression of the central nervous system. Prolonged skin contact causes dermatitis.

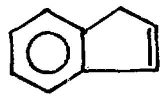
Allylbenzene (3-Phenylpropene) $C_6H_5CH_2CH=CH_2$



Allylbenzene is a liquid synthetic fuel. No human data have been found.

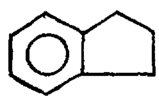
Indene and Indan

Indene (C_9H_8)



Indene is a colorless liquid. Its chief use is in the preparation of cumarone-indene resins. Inhalation of indene is expected (by analogy of related monoaromatic hydrocarbons) to cause irritation of mucous membranes, but no quantitative studies on human inhalation of indene vapors have been reported. Prolonged or repeated skin contact with liquid indene has a defatting action on the skin and may lead to dermatitis. Studies on animals suggest possible inhalation toxicity (1).

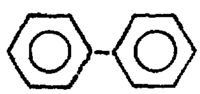
Indan C_9H_{10}



No human data found.

Diaromatic Hydrocarbons

Biphenyl (Diphenyl, Phenylbenzene) $C_6H_5C_6H_5$



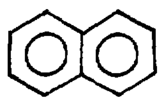
Biphenyl exists as white scales with a pleasant peculiar odor. Crystalline forms are also known. Because of its thermal stability, biphenyl is used as a heat-transfer agent, either alone or mixed with diphenyl oxide. It is also used as a fungistat in the shipping of oranges and in organic syntheses.

Biphenyl is not particularly toxic by ingestion. Mild to moderate eye irritation was reported by workers exposed to the fume of an unknown concentration.

A few cases of occupational biphenyl poisoning have been reported. Transient nausea, vomiting, and bronchitis were reported in workers exposed to biphenyl vapors during paper impregnation. Poor hygienic condition in another factory (concentration of biphenyl from 4.4 to 128 mg/m^3) resulted in poisoning characterized by peripheral nerve injury and liver damage. One case of death resulted from acute liver atrophy. In still another plant, electroencephalic and electromyographic abnormalities were observed (1).

No threshold for safe worker exposure can be estimated from the currently available data. Studies on animals suggest a TLV of 0.2 ppm an STEL of 0.6 ppm until evidence indicating the need for a change is available.

Naphthalene ($C_{10}H_8$)



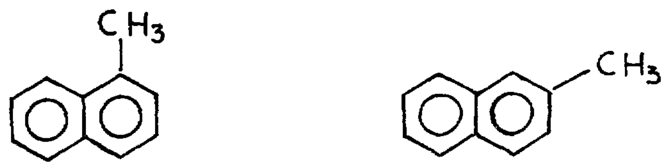
Naphthalene occurs commonly as white crystalline flakes which have a strong coal tar odor. Naphthalene is used in the household as a moth repellent; scientifically it is used in scintillation counters. Naphthalene represents raw material used for the manufacture of several derivatives. It is also used in the production of dyes, explosives, lubricants, tanning agents, and emulsion breakers.

Skin contact with naphthalene produces severe dermatitis. Inhalation of naphthalene vapors may cause headache, nausea, and sweating. Injuries of the cornea and optical neuritis, kidney damage, dysuria, and hematuria have been reported. Blankets containing naphthalene have been known to cause acute hemolysis in infants, in some cases fatal (1).

Inhalation may produce hemolytic symptoms in persons with the red cell glucose-6-phosphate dehydrogenase deficiency. Hemolysis is accompanied by anemia, leucocytosis, fever, hemoglobinuria, renal insufficiency, jaundice, and disturbances in liver function. Symptoms often begin on the third day after ingestion. Bone marrow may appear hyperplastic. Death can occur from respiratory failure. The lethal doses are 2-3 g (children) and 5 to 15 g (adult).

Ingestion of naphthalene causes abdominal cramps, vomiting, and diarrhea; listlessness and confusion and coma with convulsions may follow in severe poisonings. Irritation of the urinary bladder is presumably due to the excretory products of naphthalene metabolism.

Methylnaphthalene $C_{10}H_7CH_3$



α β

Methyl- and dimethylnaphthalenes occur in coke-oven tar and in certain petroleum fractions. Separation of individual isomers seldom is attempted in the USA. The mixtures are used as solvents for pesticides, sulfur, various aromatic compounds, and in dyeing of synthetic fibers (27A). Limited animal experiments suggest high toxicity. No human data found.

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RAC 14	SYSTEM											EFFECT							
MONO/DIAROMATIC HYDROCARBONS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Toluene $C_6H_5-CH_3$	X		X		?			X	X								X	X	
Xylene $C_6H_4(CH_3)_2$	X		X		X	X	X	X	X		X						X		
Ethyl Benzene $C_6H_5C_2H_5$		X	X		?			X			?						X		
Cumene $C_6H_5CH(CH_3)_2$			X					X	X								X	X	
Styrene $C_6H_5CHCH_2$								X	X				?	?			X		
α Methyl Styrene $C_6H_5(CH_3){=}CH_2$			X					X	X		?						X		
Allylbenzene C_6H_5 $CH_2CH{=}CH_2$	No human data found																		
Indene C_9H_8			X					X									X		
Indan C_9H_{10}	No human data found																		
Biphenyl $C_6H_5C_6H_5$		X				X		X	X		X						X		
Naphthalene $C_{10}H_8$			X		X	X	X	X	X								X		
Methylnapthalene $C_{10}H_7CH_3$	No human data found																		

X = known human effect

? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #15 - POLYCYCLIC AROMATIC HYDROCARBONS

Overview

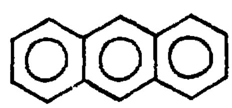
Polycyclic aromatic hydrocarbons (PAH) are a group of hydrocarbon compounds with three or more benzene rings. They are present in coal and are formed during the combustion of hydrocarbon fuels.

Polycyclic aromatic hydrocarbons reviewed in RAC #15 include 51 compounds. These are grouped into six subcategories.

1. Tricyclic hydrocarbons
2. Tetracyclic hydrocarbons (benzo-derivatives of tricyclics)
3. Pentacyclic hydrocarbons (dibenzo-derivatives of tricyclics and benzo-pyrenes)
4. Hexacyclic hydrocarbons (dibenzo-derivatives of pyrene, benzo-perilene, and dibenzo-naphthacenes)
5. Fluorene, fluoroanthene and its benzo-derivatives
6. Methyl and dimethyl derivatives of polycyclic hydrocarbons

Tricyclic Hydrocarbons ($C_{14}H_{10}$)

Anthracene



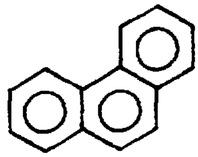
Anthracene is obtained from coal tar and used mainly in the manufacture of dyes. Coal tar fumes contain mainly anthracene and phenanthrene (44).

Anthracene causes acute and chronic dermatitis, and phototoxic and photoallergic action on the skin. Exposure to anthracene has produced skin cancers on the arms and the scrotum, reported in the earliest studies of chimney sweeps.

Internal absorption of coal tar fraction can cause headache and nausea. Prolonged exposure can lead to gastrointestinal inflammation (48D).

Eye contact with anthracene can cause photophobia, and edema of the eyelids, but symptoms disappear after cessation of contact.

Phenanthracene (Phenanthrene)



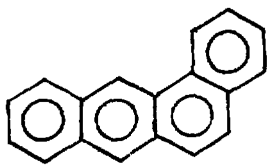
Phenanthracene is a constituent of waste industrial water, airborne tobacco smoke, and car exhaust.

It is a mild allergen and mild human dermal photosensitizer.

Weak dermal neoplastic properties were reported in animal studies (49B).

Tetracyclic Hydrocarbons

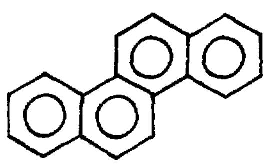
Benz[a]anthracene (BaA; 1,2-Benzanthracene, 2,3-Benzophenanthracene, Naphanthracene, Tetraphene) $C_{18}H_{12}$



Benz[a]anthracene is a constituent of cigarette smoke, car exhaust, soot, coal gas, and electric plant emissions. Microgram quantities are found in barbecued and smoked food and in roasted coffee.

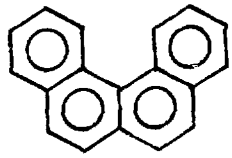
It is an animal carcinogen (58A, 68). Many carcinogenic PAHs are derived from the BaA skeleton (48D).

Chrysene (1,2-Benzophenanthrene, Benzo[a]phenanthrene, 1,2,5,6,-Dibenzonaphthalene) $C_{18}H_{12}$



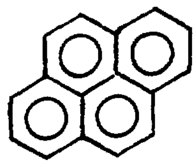
Chrysene is a weak skin carcinogen in animals. It is toxic by oral, dermal, eye, and inhalation routes (49A).

Benzo[c]phenanthrene (3,4-Benz[o]phenanthrene, 3,4-Benzphenanthrene) $C_{18}H_{12}$



Benzo[c]phenanthrene is considered to be a relatively weak animal carcinogen present in the atmosphere (49).

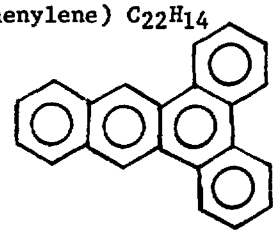
Pyrene (Benzo[d,e,f]phenanthrene) $C_{16}H_{10}$



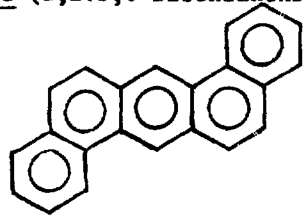
Animal carcinogen.

Pentacyclic Hydrocarbons

Dibenz[a,c]anthracene (1,2,3,4-Dibenzanthrecene, Naphtho-2,3:9,10 Phenanthrene, Benzo[b]triphenylene) $C_{22}H_{14}$

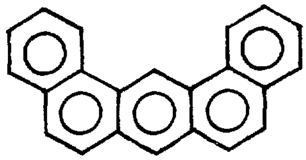


Dibenz[a,h]anthracene (1,2:5,6-Dibenzanthracene; DB (a,h)A) $C_{22}H_{14}$

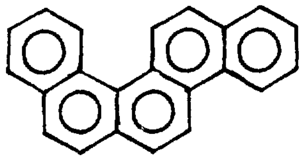


Highest concentrations are reported in soot (64 to 705 mg/1000 m^3) and in coal tar (230 ng/kg). Animal carcinogen and tumorigen.

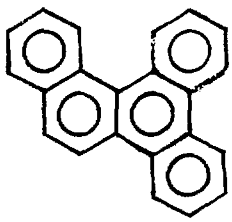
Dibenz[a,j]anthracene (1,2:7,8-Dibenzanthracene, Dinaphthano-anthracene) $C_{22}H_{14}$



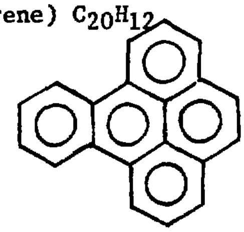
Benzo[c]chrysene (1,2:5,6-Dibenzophenanthrene) $C_{22}H_{14}$



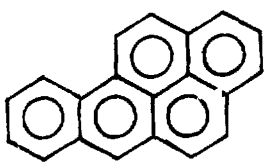
Benzo[g]chrysene (1,2:3,4-Dibenzophenanthrene) $C_{22}H_{14}$



Benzo[e]pyrene (1,2-Benzopyrene) $C_{20}H_{12}$



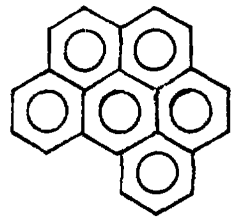
Benzo[a]pyrene (BaP; 3,4-Benzopyrene) $C_{20}H_{12}$



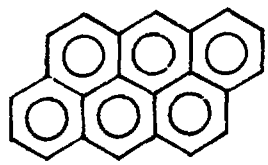
Usually found in the air surrounding urban and industrial areas and occasionally in water samples, benzo[a]pyrene is recognized as a powerful animal carcinogen and is strongly suspected as a human carcinogen. Heavy BaP exposure has been correlated with increase in lung cancer incidence, but fumes from emissions also contain other compounds which may influence lung cancer directly, or may produce a synergistic effect with BaP. Originating from fossil fuel and other organic combustion processes, BaP is largely adsorbed on fine air particulates and hence is a widespread atmospheric pollutant. Since BaP is readily identifiable, it is frequently used as an index of PAH compounds.

Hexacyclic Hydrocarbons

Benzo[g,h,i]perylene ("tiger butter") $C_{22}H_{12}$

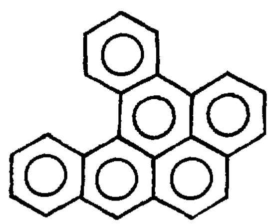


Dibenzo[a,h]pyrene (Dibenzo[b,d,e,f]chrysene; 1,2:6,7-Dibenzopyrene; 3,4,8,9-Dibenzopyrene) $C_{22}H_{14}$



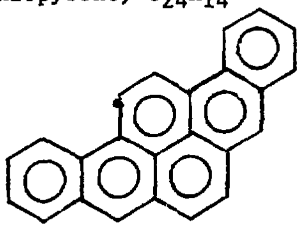
Listed as suspected human carcinogen on the basis of animal studies.

Dibenzo[a,l]pyrene (Dibenzo[d,e,f,p]chrysene) $C_{24}H_{14}$



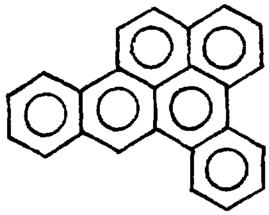
Animal carcinogen.

Dibenzo[a,i]pyrene (Benzo[r,s,t]pentaphene; DB(a,i)P; 1,2,7,8-Dibenzopyrene; 3,4:9,10-Dibenzopyrene) $C_{24}H_{14}$

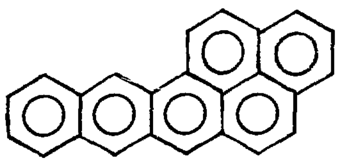


Animal carcinogen.

Dibenzo[a,e]pyrene (1,2:4,5-Dibenzopyrene; Naphtho[1,2,3,4-d,e,f] chrysene; DB(ae)P) $C_{24}H_{14}$



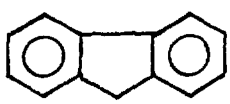
Naphtho(8,1,2-c,d,e)naphthacene (Naphtho-2,3, a-Pyrene) $C_{22}H_{14}$



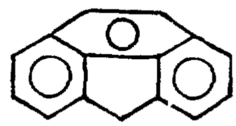
Dibenzo[a,c]naphthacene (1,2:3,4-Dibenzonaphthacene; 1,2:3,4-Dibenzotetracene) $C_{24}H_{16}$

Fluorene

Fluorene $C_{13}H_{10}$



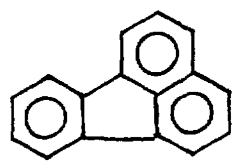
Benzo(d,e,f)fluorene (4,5-Methylenephenanthracene, 4,5-Phenanthrylene Methane) $C_{15}H_{10}$



Strong carcinogen when applied to mouse skin.

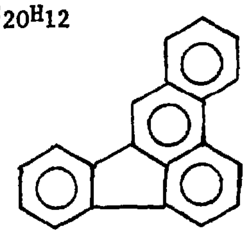
Fluoroanthene and its Benzo-Derivatives

Fluoroanthene (1,2-Benzacenaphthene, Idryl) $C_{16}H_{10}$

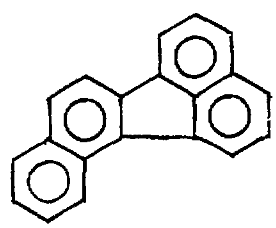


Limited animal studies show no toxicity.

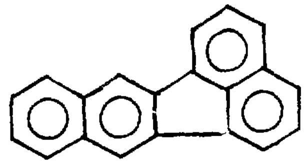
Benzo(b)fluoroanthene (3,4-Benzofluoroanthene, Benz(e)-acephenanthrylene) $C_{20}H_{12}$



Benzo(j)fluoroanthene (10,11-Benzofluoroanthene) $C_{20}H_{12}$



Benzo(k)fluoroanthene



Methyl and Dimethyl Derivatives of Polycyclic Hydrocarbons

Tricyclic Derivatives $C_{15}H_{12}$

1 - Methylanthracene

2 - Methylanthracene

9 - Methylanthracene

Methylphenanthrene

1,4 - Dimethylphenanthrene

1,8 - Dimethylphenanthrene

2,7 - Dimethylphenanthrene

3,6 - Dimethylphenanthrene

4,5 - Dimethylphenanthrene

9,10 - Dimethylphenanthrene

Tetracyclic Derivatives

1 - Methylchrysene $C_{19}H_{14}$

2 - Methylchrysene $C_{19}H_{14}$

6 - Methylchrysene $C_{19}H_{14}$

Methylpyrene

Pentacyclic Derivatives

Methylbenzo[e]pyrene

1 - Methylbenzo[a]pyrene $C_{21}H_{14}$

6 - Methylbenzo[a]pyrene

10 - Methylbenzo[a]pyrene

11 - Methylbenzo[a]pyrene

12 - Methylbenzo[a]pyrene

Fluorene Derivatives

1 - Methylfluorene

2 - Methylfluorene

3 - Methylfluorene

4 - Methylfluorene

9 - Methylfluorene

It has generally been concluded that PAHs are important agents in associations of human cancer with cigarette smoking and exposure to soot, raw shale oils, roofing tar and coke oven, gas retort, and coal liquefaction emissions. These conclusions are generally based on epidemiological studies of the total exposure to a complex mixture (38). Animal studies and in vitro mutagenesis test systems have also played an important role in interpretation. (Refer also to RACs 29 and 30.)

Health effects of PAH were extensively reviewed in the National Academy of Science committee reports in 1972 and 1976. While there has been considerable new laboratory work since that time and limited new epidemiological data, basic clinical and epidemiological understanding of health effects of PAH is unchanged.

Quantitative Dose Response

Two basic sources of quantitative dose-response information have been studies of public exposure and studies of occupational exposure. Exposure indices used have been benzo[a]pyrene (BaP) and total benzene soluble particulate matter. The latter may include non-PAH compounds. Myers et al. (48B) are more explicit than most authors by stating their estimates are "For continuous inhalation of air with a mixture of combustion products containing 1 ng of benz-a-pyrene (BaP) per m^3." Public exposure includes correlation analysis of lung cancer and ambient BaP concentrations (48C) and more general urban pollution studies and cigarette smoking using BaP as an index of exposure (17A). These estimates are summarized in Table 1.

The earliest quantitative dose-response function was based on studies of British gas retort workers (17B, 39A, 50A). A number of quantitative dose-response functions have been derived from data generated in the Long-Term Steelworkers Mortality Study at the University of Pittsburgh Graduate School of Public Health (53). The estimates are given in Table 2 indexed by BaP.

A comparison of Tables 1 and 2 shows that estimates derived from general population studies are about 10 times higher than those derived from occupational studies. The occupational studies are of much better defined populations and are generally more reliable studies. Both the occupational and general public studies may be incompatible with a linear dose-response relationship implied by the coefficients in the tables. The

Table 1. General Population Studies

Study	Annual Fatal ca/million person-ng BaP/m^3
NAS (48C)	17
Cuddihy et al. (17A)	14-40
Myers et al. (48B)	10-40
Ozkaynak et al. (49A)	0-40

Table 2. Occupational Population Studies

Study	Annual Fatal ca/million person-ng BaP/m^3
Pike et al. (50A)	4
Land (1976)	2.2*
Cuddihy (17A)	0.8
EPA CAG (19A)	2.3
Morris and Thode (48A)	0.5*
Battelle Northwest (1982)	0.9*
Brown (9A)	0.02*

*Indicates transformed from original form (original usually lifetime cancers per coal tar pitch volatiles exposure).

overall range of available estimates is best expressed by Ozkaynak et al. (49A) as 0 to 40 annual fatal cancers per million person-ng BaP per cubic meter.

In one study in which a quantitative risk estimate was used to predict cancers in a population associated with organic air pollutants (50A), cancer cases were later followed epidemiologically (50A). It was concluded that occupational exposure could account for all the excess cancer mortality. This suggests less credit should be given to higher risk estimates and that zero is a possible estimate for exposures at low ambient exposures.

Metabolism

Polycyclic aromatic hydrocarbons belong to a group of carcinogens which are not chemically reactive with cellular components of living organisms. They must be converted metabolically into compounds which are capable of reacting directly with the macromolecules of the cell (48C,35).

Benzo[a]pyrene is therefore a procarcinogen which is metabolized by animal and human cells into derivatives, proximate and ultimate carcinogens. A variety of metabolites was found in different types of tissues (9,16).

The primary enzyme system responsible for the metabolism of polycyclic hydrocarbons is localized in the microsomal fraction of living cells. This enzyme system called "aryl hydrocarbon hydrolaze" is responsible for the conversion of benzo[a]pyrene into cytotoxic metabolites and for their binding to cellular DNA or protein.

The metabolism and carcinogenicity of BaP have been studied in animals _in vivo_ and in cultures _in vitro_ of organs, cells, and cell-free fractions. The parallelism between organ's response in animals _in vivo_ and _in vitro_ have been demonstrated (48C). Human data are obtained from organs, cells, and microsomal fractions cultured _in vitro_. Quantitation of BaP metabolites, their binding to cellular DNA, and the production of mutagenetic effects are evaluated after exposure of cultures to BaP.

Comparisons of human and animal tissues indicate basically similar effects of BaP, although some differences in the proportions of metabolites or mutations induced by BaP have been reported (7,9,12,22,30,32-34,45,46, 48,50,56).

The differences between different types of human tissues in their reactions to carcinogens have also been recognized. The urinary bladder seems to be the most sensitive to carcinogenic effect of BaP with the following sequence of skin, bronchus, esophagus, and colon (5,6,59,64). The binding of BaP metabolites in epithelial cells is more prominent than the binding in fibroblasts (4). The main metabolic pattern of BaP was different in epithelial cells and in fibroblasts (9,62).

Cultured in vitro cells and tissues taken from different persons show great individual variations in the metabolism of BaP, as reported in breast cells (23), esophagus (25), neoplastic lung tissue (15,43) and microsomal fractions from lung neoplasm (63) and liver cells (19). Prominent variations in placental BaP metabolism of cigarette smokers were reported (24). Binding of BaP to DNA in cultured human endometrial tissues was substantially higher in premenopausal than postmenopausal women (18,42). These findings correlate with studies suggesting that carcinogenic factors such as cigarette smoke, polycyclic and polyhalogenated hydrocarbons induce special enzymes which activate estrogens and nonsteroid antiestrogens to act as initiators and/or promoters of neoplasia in estrogen-dependent organs (67).

A genetic factor is also involved in the individual differences in the resistance to carcinogen. Comparison of BaP metabolism in human hair follicles showed that monozygotic twins display smaller differences than heterozygotic twins and that great individual differences occur within pairs of unrelated persons (32).

The formation of DNA adducts in the cell can be stimulated by other factors such as lipoproteins which show high levels of binding of BaP and its metabolites (11,17,54,60,61).

On the other hand, A retinoids (vitamin A and its precursors) reduce the carcinogenic effect of BaP and its metabolites by inhibition of the neosynthesis of enzymes which metabolize BaP (39,55,58,60). Prominent inhibitory effect and suppression of neoplasms was also achieved by the addition of seven synthetic phenolic compounds to the diet of mice which had BaP-induced neoplasia. Three naturally occurring phenolic derivatives of cinnamic acids had similar inhibitory effects (69). The inhibition of BaP metabolism in human liver microsomes has also been achieved by the addition of naturally occurring flavonoids. Twelve flavonoids, all possessing the hydroxyl groups, showed the inhibitory effects. However, three flavonoids that lacked hydroxyl groups caused the many-fold stimulation of BaP and of aflatoxin B_1 metabolism (10). Cultured human skin fibroblasts originating from donors with glucose-6-phosphate deficiency were more resistant to BaP than normal human skin fibroblasts (21,51). Altered glucose metabolism resulting in a decrease of NADPH/NADP ratio inhibited benzo[a]pyrene whose activation proceeds through the NADPH-dependent enzyme formation (21,51).

The tests of mutagenic activity of different compounds are commonly carried out on Salmonella typhimurium (the Ame's test). It has been reported, however, that chemicals nonmutagenic to S. typhimurium can induce morphologic transformations in Syrian hamster embryo cells (2). Mutagenic effect of BaP on Salmonella has been enhanced by the addition of other chemicals (27,29,41,47,52,57,65). Human hepatoma cells treated with benz(a)anthracene yielded an increased frequency of sister chromatid exchanges (SCEs) when exposed to benzo[a]pyrene (1). Also, an enhanced metabolic activity of BaP in cultured normal and neoplastic human cells was induced by the pretreatment of the culture with other chemicals (13,14,20, 29,31,33,37,57). The pretreatment of bronchial epithelial cells with benz(a)anthracene enhanced metabolic activity of BaP in mice but not in human cells, thus indicating that animal model systems for PAH carcinogenesis in man have to be selected on the basis of comparable metabolite patterns (34). Metabolic activity of BaP can also be enhanced by such factors as Herpes simplex virus (4,36), by the automobile exhaust products (8,28,40,41), and by other airborne particles (3,66).

Polycyclic aromatic hydrocarbons occur as a mixture of airborne particles. Herlan and Mayer (26), reviewing the difficulties involved in determining exact structures of polycyclics in environmental samples, asked if it was ingenuous to maintain the principle of analyzing individual compounds.

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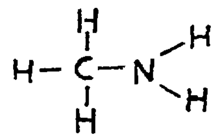
RAC 15	SYSTEM											EFFECT							
POLYCYCLIC AROMATIC HYDROCARBONS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Tricyclic $C_{14}H_{10}$			X			X		X				X				X	X		
Tetracyclic $C_{18}H_{12}/C_{16}H_{10}$			X					X				?							
Pentacyclic $C_{22}H_{14}/C_{20}H_{12}$		X	X			X	?	?				X		X	?				
Hexacyclic $C_{22}H_{12}/C_{22}H_{14}/C_{24}H_{14}$ $C_{24}H_{16}$												?							
Fluorene $C_{13}H_{10}$; and its Benzo-derivatives			?									?							
Fluoranthene $C_{16}H_{10}$ and its Benzo-derivatives	No human data found																		
Methyl Derivatives of Polycyclic Hydrocarbons	No human data found																		

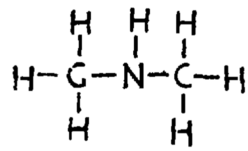
X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

The four compounds reviewed in this category are:

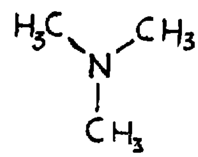
Methylamine (Aminomethane) CH_3NH_2



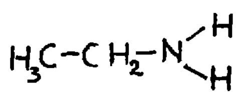
Dimethylamine $(CH_3)_2NH$



Trimethylamine $(CH_3)_3N$



Ethylamine $C_2H_5NH_2$



Aliphatic amines are the alkyl derivatives of ammonia. They are organic solvents with an ammonia-like odor. With the exception of ethylamine, they are gases under ordinary conditions (room temperature) and become colorless liquids when cooled or compressed. Ethylamine remains a gas when pressurized (1-8).

In workers exposed to these compounds, varying concentrations have been found in the urine. Other than being strong eye, lip, skin, and upper respiratory tract irritants, no other adverse health effects were found for this group of compounds (1-8).

A TLV of 10 ppm has been set for all four compounds covered in this group, to prevent eye and mucous irritation and severe tissue damage that might occur at higher doses (based on animal studies) (1).

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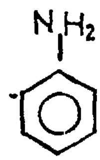
RAC 16	SYSTEM											EFFECT							
ALIPHATIC AMINES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Methylamine CH_3NH_2			X					X									X		
Dimethylamine $(CH_3)_2NH$			X					X									X		
Trimethylamine $(CH_3)_3N$			X					X									X		
Ethylamine $C_2H_5NH_2$			X					X									X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #17 - AROMATIC AMINES (EXCLUDING N-HETEROCYCLICS)

Aromatic amines are compounds in which the aromatic ring is attached to nitrogen. Aromatic amines listed in RAC #17 include phenyl and biphenyl amines (aniline and xenylamine), biphenyl diamines (hydrazobenzene and benzidine), and naphthylamines (α- and β-).

Aniline (Aminobenzene; Phenyl Amine) $C_2H_5NH_2$



Aniline is an oily liquid with a characteristic odor detectable at 1 ppm. Aniline is used chiefly in the chemical industry for the production of polymers, dyes, rubber accelerators and antioxidants, drugs (such as sulfa drugs), photographic chemicals, isocyanates, herbicides, and fungicides.

Severe intoxication with aniline may occur after skin contact or ingestion. Skin absorption of aniline vapor was evaluated as approximately equal to absorption from inhalation (1). No significant difference appeared between the mean rate of skin absorption of liquid aniline and that with 3% content of water (2). Studied in vitro, permeability of different areas of human skin to aniline varied, however, up to 100-fold (4).

Acute intoxication results in cyanosis, caused by the conversion of hemoglobin to methemoglobin. As the methemoglobin content rises above a certain level, death ensues from anoxia (1, 3, 8). Methemoglobinemia and hemolytic anemia have been reported in two patients using phenazopyridine. The probable role of aniline, a major metabolite of phenazopyridine, was discussed (6).

Chronic poisoning can occur after repeated exposures to low concentrations. Early symptoms are pallor, secondary anemia, and fatigue. Such cases recover when properly treated and completely removed from further exposure (8).

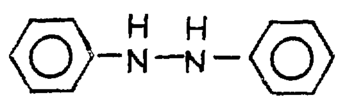
In human blood lymphocytes, aniline did not induce an increase of sister chromatid exchange in vitro, but such an increase was induced by p-aminophenol, one of the aniline metabolites in the body (14).

Xenylamine (4-Aminodiphenyl, 4-Diphenylamine) $C_6H_5NHC_6H_5$

Xenylamine is composed of colorless crystals. It is no longer produced on a commercial scale because of its demonstrated carcinogenicity. It appears to be one of the most potent known bladder carcinogens.

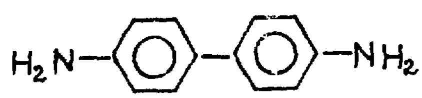
Epidemiologic studies conducted between 1935 and 1969 by Melick and co-workers confirmed a high incidence of bladder tumors among exposed workers. The tumors appeared 5 to 19 years after initial exposure, which ranged in duration from 1 to 10 years. No dose relationship was given (1, 5, 12).

Hydrazobenzene (1,2-Diphenylhydrazine) $C_6H_5(NH)_2C_6H_5$



Hydrazobenzene is a precursor of benzidine and therefore a potential carcinogen. Carcinogenicity of hydrazobenzene was found in animal studies. It is listed as human carcinogen (12). No human data have been found.

Benzidine (4,4'-Diaminobiphenyl) $NH_2C_6H_4-C_6H_4NH_2$



Benzidine is a white or slightly reddish crystalline material which darkens on exposure to light and air. Its major industrial use is in the preparation of dyes. It is also used in laboratories as a reagent or indicator in forensic and clinical medicine, and for the detection of hydrogen peroxide in milk. There is some use in security printing, in the detection of HCN and sulfate, and for determination of nicotine.

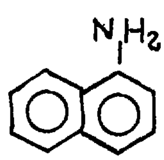
Benzidine is a well-recognized carcinogen. There are a large number of reports of bladder cancer in humans caused by benzidine in the industrial environment. Both inhalation and skin absorption are significant portals of entry for benzidine into the human body. Ingestion of benzidine has occurred in industries producing vapors, aerosols, fumes, and dust. A long-term study of workers in the manufacture of benzidine by Zavon et al. (17) demonstrated that 13 of 25 exposed men developed bladder tumors, 11 of which were malignant. In three cases, malignant tumors metastasized to the kidney, and metastases to the neck and abdomen were also recognized. The periods of exposure to benzidine ranged from 8 to 28 years (average 13.61). Tumorigenic action of benzidine shows long latency. In the above study, tumors appeared 9 to 29 years (average 16.62) after the first exposure. Benzidine-based dyes containing benzidine attached to other substituents by diazo linkages are also highly carcinogenic, since they are metabolized to carcinogen-benzidine.

Epidemiologic studies (15, 16), indicate an association between employment in the dye industry and urinary bladder cancer in humans. However, the average latent period from the first and last exposure was 26.4 and 14.0 years, respectively. Thus, lifetime urine cytology surveillance is strongly recommended for all exposed workers (16).

Bladder tumors have also been reported among Japanese silk painters who were believed to have ingested small amounts of benzidine dyes on a regular basis over many years (8).

Regulations concerning the handling of known carcinogens have been imposed in most industrial nations. U.S. regulations caused virtually all the dye companies to discontinue the use of benzidine compounds. All countries which list benzidine as an industrial health hazard consider it a carcinogen. None has adopted a limit for concentration in workroom air (1, 8).

<u>1-Naphthylamine (α-Naphththylamine, 1-Aminonaphthalene)</u> $C_{10}H_7NH_2$



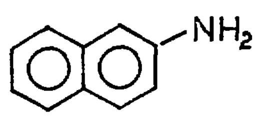
1-Naphthylamine occurs as needles or a crystalline mass becoming red on exposure to air. It has an unpleasant odor. α-Naphthylamine has been declared by the FDA as a carcinogen. IARC Monographs report 93 cases of bladder tumors attributed to α-naphthylamine. The latent period was 5 to over 50 years with the average time about 18 years (10).

Epidemiologic studies of a large cohort of workers in industries manufacturing benzidine and α-naphthylamine in Japan revealed that primary cancers of the genitourinary organs were often followed by subsequent primary cancers of the liver, gall bladder, bile duct, large intestine, and lung (9).

Since commercial 1-naphthylamine contains 4 to 10% impurities of 2-naphthylamine, it is unclear whether or not bladder cancer reported in the occupational exposure was due to the impurity. There are no human data available on exposure to pure 1-naphthylamine (5).

Studies on dogs given various mixtures of 1- and 2-naphthylamines claimed no carcinogenic effect of 1-naphthylamine (13).

2-Naphthylamine (β-Naphthylamine, 2-Aminonaphthalene) $C_{10}H_7NH_2$



2-Naphthylamine forms white or reddish crystals. It is rarely used for industrial research purposes and has no commercial value. 2-Naphthylamine was widely used in dyestuff, and rubber, and in research in the past years, but it has been banned because of its very high carcinogenicity. It is considered the most dangerous carcinogen among aromatic amines. Acute exposures can cause methemoglobinemia or hemorrhagic cystitis. Contact with 2-naphthylamine should be avoided. A worker handling this substance should be fully protected with impervious clothing and self-contained breathing equipment. In addition, the hands, feet, and eyes should be covered. No exposure by any route should be permitted (1).

The average latent period of carcinogenic activity is 16 years. Recent long-term studies of Yamaguchi et al. (16) state that it may be 26.4 years or more.

The use of the Coil Planet Centrifuge system in studies of the effects of aromatic nitro and amino compounds on rabbit red blood cells (RBC) showed the increase in methemoglobin, appearance of Heinz bodies, and an increased osmotic fragility of RBC. The use of the Coil Planet Centrifuge method is suggested in examining workers exposed to aromatic and nitro amino compounds (11).

A method was developed for the removal of carcinogenic aromatic amines from industrial aqueous effluents. It includes the treatment of aqueous solutions containing the carcinogens with horseradish peroxidase and hydrogen peroxide (7).

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RAC 17	SYSTEM											EFFECT							
AROMATIC AMINES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Aniline $C_2H_5NH_2$			X		X												X		
Xenylamine $C_6H_5NHC_6H_5$							X					X							
Hydrazobenze $C_6H_5(NH_2)_2C_6H_5$							?					?							
Benzidine $NH_2C_6H_4-C_6H_4NH_2$							X					X							
1-Naphthylamine $C_{10}H_7NH_2$							X					X							
2-Naphthylamine $C_{10}H_7NH_2$					X		X					X							

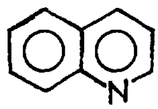
X = known human effect

? = based on animal data, experience with similar compounds, or inconclusive human data

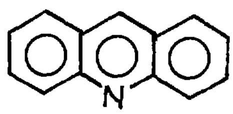
RAC #18 - ALKALINE NITROGEN HETEROCYCLICS

The three compounds reviewed in this category are:

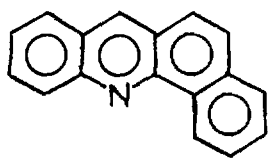
Quinoline (C_9-H_7N)



Acridine (C_{13}-H_9-N)



Benz(c)acridine (C_{17}-H_{11}-N)



Quinoline, acridine and benz(c)acridine occur in small amounts in coal tar (5). The primary effects of exposure to these compounds were skin and mucous membrane irritation (2,6). No industrial injuries related to exposures were found, but a notation in Toxicology Data Bank (taken from the Encyclopedia of Occupational Health and Safety, 1971, p. 1,136) states "Clinical signs of toxicity to 'Quinoline' include lethargy, respiratory distress, and prostration leading to coma." In addition, quinoline is classified as an animal mutagen and tumorigen (3). Recently acridine has been detected in the urine of patients whose skin has been painted with a paste containing 1-6g of coal-tar (a dermatologic therapeutic agent). This observation was the first proof of the absorption of coal-tar component through the skin (1).

Since this group of compounds is found in coal tar (a known carcinogen), the role they play (if any) in the carcinogenic properties of coal tar is unknown at this time, but they are included in the NIOSH list of suspected carcinogens.(4)

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RAC 18	SYSTEM											EFFECT							
ALKALINE N HETEROCYCLICS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Quinoline C_9H_7N		X	X					X	X			?					X		
Acridine $C_{13}H_9N$			X					X				?					X		
Benz(c)Acridine $C_{17}H_{11}N$			X					X				?					X		

X = known human effect

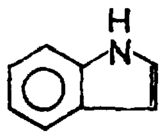
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #19 - NEUTRAL N, O, S HETEROCYCLICS (EXCLUDING "VOLATILES")

Nitrogen, oxygen, and sulfur heterocyclics are characterized by the N, O, or S atoms as members of aromatic rings. Neutral heterocyclics selected for RAC #19 include the following:

Nitrogen Heterocyclics

<u>Indole (1-Benzo[b]pyrrole; 2,3-Benzopyrrole, 1-Aza Indene; 1-Benzazole)</u> C_8H_6NH

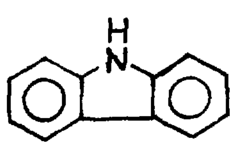


Indole forms leaflets with an intense fecal odor. It is found in a large number of naturally occurring compounds (e.g., jasmine and orange blossom oils). It is of a commercial importance as a component of perfumes. The commercial source of indole is the extraction from coal-tar distillate.

Indole derivatives occur as essential amino acid (tryptofan), as plant growth hormone, and as several groups of important alkaloids. 3-Methylindole is produced with indole during digestion and decomposition of proteins, and hence both occur in the intestines and feces. Recent medicinal and biochemical studies on indole derivatives were focused on serotonin (a metabolite of brain chemistry); psychotomimetic indoles; the tranquilizer reserpine; and the melamin pigments (2).

No data on the effects of indole on human health have been found.

<u>Carbazole (9H-Carbazole; 9-Azafluorene; Dibenzopyrrole; Diphenylemimine)</u> $C_{12}H_8NH$

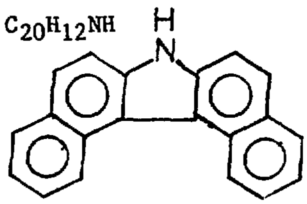


Carbazole occurs as crystals. It is used as a dye intermediate, in making photographic plates sensitive to ultraviolet light, and as a reagent for lignin, carbohydrates, and formaldehyde.

Carbazole at 0.6, 0.3, and 0.15% in the diet of mice appeared significantly carcinogenic to the liver and forestomach (4).

Carbazole is listed by Sax (3) as an allergen, but otherwise no data about its effect on human health have been found.

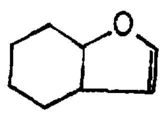
7H-Dibenzo (C_9) carbazole, $C_{20}H_{12}NH$



7H-Dibenzo (C_9) carbazole has been found in cigarette tar. It is carcinogenic in humans. No case reports or epidemiological studies on the significance of the exposure of man to 7H-dibenzo (C_9) carbazole have been found (1).

Oxygen Heterocyclic

Benzofuran (Cumarone) C_8H_6O

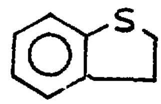


Benzofuran is isolated from coal tar oils. It is an oil of aromatic odor, used in the manufacture of cumarone-indene resins.

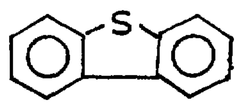
No data on the effect of benzofuran on human health were found.

Sulfur Heterocyclics

2,3-Benzothiophene



Dibenzothiophene (Diphenylene Sulfide)



No data on the effect of S heterocyclics on human health were found.

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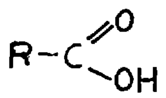
RAC 19	SYSTEM											EFFECT							
NEUTRAL N, O, & S HETEROCYCLICS (Excluding "Volatiles")	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Indole C_8H_6NH	No human data found																		
Carbazole $C_{12}H_8NH$																X			
7H-Dibenzo Carbazole $C_{20}H_{12}NH$	No human data found																		
Benzofuran C_8H_6O	No human data found																		
2,3-Benzothiophene	No human data found																		
Dibenzothiophene	No human data found																		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #20 - CARBOXYLIC ACIDS (EXCLUDING "VOLATILE")

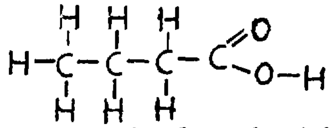
Carboxylic acids contain a carboxyl group



attached to aliphatic or aromatic hydrocarbons. These substances ionize in water to give acidic solutions and can combine to form esters, amides, or anhydrides (2). Carboxylic acids derived from open-chain hydrocarbons with more than six carbon atoms are often referred to as fatty acids. They can be obtained from natural sources such as animal tallow and greases, and various vegetable and marine oils. Carboxylic acids are also produced synthetically from petroleum sources (9). Two aliphatic and two aromatic carboxylic acids will be discussed in this category.

Aliphatic Carboxylic Acids

Butyric Acid (Butanoic Acid) $CH_3(CH_2)_2COOH$

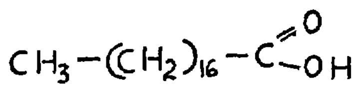


Butyric acid is a colorless oily liquid with an unpleasant rancid odor. Butter contains about 4 to 5% butyric acid. Butyric acid is used in the manufacture of esters, some of which serve as bases in artificial flavoring ingredients of liquers, soda water, syrups, and candies. It is also used for varnishes and as a decalcifier of hides (10).

Butyric acid is an eye, skin, and respiratory irritant and requires strict handling precautions (5). An application of butyric acid to intact human skin may be followed within an hour by moderate burning; within 24 hours, a slight scaling of the epidermis may occur (17). Butyric acid has been noted to have antiseptic properties (17) and has been suggested for use as an anticancer agent. In the latter role, sodium butyrate was given to patients with neuroblastoma. Although high doses were given (up to 10 g/day), no clinically detectable toxicity was observed (14).

In vitro studies of normal and Xeroderma pigmentosum human fibroblasts showed that the pretreatment with sodium butyrate produced a decrease in UV-induced DNA replicative synthesis and an increase in DNA repair synthesis (16). Another study showed that sodium butyrate (and several other compounds) were cytotoxic to actively cycling cells of human leukemic lymphoblasts (1). Treatment of human lymphoblastoid cells with butyrate and 5'-bromo-deoxyuridine caused a substantial increase in Sendai virus-induced interferon synthesis. The effect was highly specific as the majority protein synthesis remained unaffected (15).

<u>Stearic Acid (Octadecanoic Acid)</u> $CH_3(Ch_2)_{16}COOH$

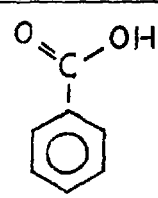


Stearic acid occurs as a glyceride in tallow and other animal fats and oils as well as in some vegetable oils (10). Stearic acid is used in candles, phonograph records, insulators, cosmetics, and coatings for bitter remedies (10), and is considered a safe food additive and gum base (13).

Stearic acid is relatively nontoxic (7) and is a mild skin irritant. An exposure of 75 mg over 3 days causes mildly toxic effects (11). Skin contact with molten stearic acid may cause an itchy dermatitis with dryness of the skin, fissures, and desquamation (17). The probable oral lethal dose for humans is in excess of 2 g/kg (more than 1 quart for a 150-lb person), with the greatest danger being from intestinal obstruction (4). Overheated wax may decompose, releasing vapors which can irritate the respiratory system and cause a chemical pneumonitis (4). Patty (2nd ed.) states that despite extensive use in industry there have been no reports of injury.

Aromatic Carboxylic Acids

<u>Benzoic Acid (Benzenecarboxylic Acid, Phenylformic Acid, Dracyclic Acid)</u> C_6H_5COOH



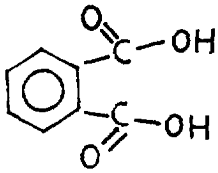
Benzoic acid occurs in nature in free and combined forms (most berries contain 0.05%). Benzoic acid is used in a wide range of preservation applications because of an effective combination of bactericidal and bacteriostatic action with nontoxicity and tastelessness. It is used as a preservative in sauces, fruit juices, bottle carbonated beverages (9), and pharmaceutical and cosmetic items such as toothpastes, powders, tobacco paste, fragrances, soap, creams, and lotions (12). It is also used in the manufacture of benzoates and benzoyl compounds, production of phenol, and dyes (10), to improve properties of alkyd resin coatings, and as an additive to coolants in automobile cooling system (9).

Healthy individuals may tolerate 0.5 g of benzoate per day in concentrations of 0.1% without ill effects, and the food content of benzoic acid is regulated by state and federal laws to be no more than 0.1% sodium benzoate (9).

Benzoic acid is a mild irritant to skin, eyes, and mucous membranes, including the nose and throat (10). The NIOSH low toxic dose for human skin is 6 mg/kg. The systemic toxicity of benzoic acid is low (9). Large doses have mainly digestive effects such as nausea and vomiting. The amount producing these symptoms may vary in different individuals from 6 to 8 g to 50 g. The probable oral lethal dose for man is 500 mg/kg (7).

Perioral urticaria was reported in children in a kindergarten following the intake and accidental perioral application of a mayonnaise salad cream. Stinging tests and closed 20-min patch tests with salad dressing were positive in a large number of healthy adult controls. Sorbic acid and benzoic acids were the components of the salad dressing which gave almost identical results. Nonimmunologic mechanisms appeared responsible for the above transient reactions and no restrictions have been suggested in the use of sorbic and benzoic acids as food preservatives (3). Dyes and food preservatives including benzoates were also recognized as components which induced food intolerance and hypersensitivity in 25 children aged 18 months to 12 years (8). No mutagenic activity has been demonstrated for benzoic acid when tested in a number of assays, and it has not been reported as a teratogenic agent (12).

Phthalic Acid (1,2-Benzenedicarboxylic Acid) $C_6H_4(COOH)_2$



Phthalic acid is a white solid with a characterisic choking odor (11). Most toxicity information is concerned with phthalate esters and phthalic anhydride. Phthalic anhydride is used in the manufacture of plasticizers, alkyl and polyester resin, synthetic fibers, dyes, pigments, pharmaceuticals, and insecticides (11).

Phthalic acid is a mild allergen and a mild irritant to the skin, eyes, and mucous membranes. There have been reports of conjunctivitis, bloody nasal excretion, atrophy of nasal mucosa, hoarseness, cough, and bronchitis in workers employed in the production of phthalic acid and anhydride (10A).

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RAC 20	SYSTEM											EFFECT							
CARBOXYLIC ACIDS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Butyric Acid $CH_3(CH_2)_2COOH$		X	X					X									X		
Stearic Acid $CH_3(CH_2)_{16}COOH$			X			X											X		
Benzoic Acid C_6H_5COOH			X			X		X								X	X		
Phthalic Acid $C_6H_4(COOH)_2$		X	X					X								X	X		

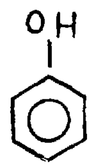
X = known human effect

? = based on animal data, experience with similar compounds, or inconclusive human data

Phenols are derivatives of aromatic hydrocarbons with a hydroxyl group attached directly to an aromatic ring. Phenols discussed in category #21 include: 1) monohydroxy benzenes [phenol C_6H_5OH; cresols (methyl phenols) $C_6H_4CH_3OH$] and xylenols (dimethyl phenols) ($C_6H_3[CH_3]_2OH$), and 2) dihydroxy benzenes ($C_6H_4[OH]_2$) (catechol, resorcinol, hydroquinone).

Monohydroxy Benzenes

Phenol (Carbolic Acid, Benzenol, Hydroxybenzene) C_6H_5OH



Phenol is a solid at room temperature and is liquefied by mixing with about 8% water. Its chief use is in the manufacture of phenolic resins and many other chemicals and drugs. It is also employed as a disinfectant in germicidal paints and as a slimicide. Phenol is produced as a waste product of many industrial activities and, as such, appears in industrial effluents that contaminate aquatic ecosystems.

Phenol is highly toxic by skin absorption, inhalation, and ingestion. However, because of its low volatility, it does not frequently constitute a serious respiratory hazard in industry (1). Formerly, use of phenol as an antiseptic in surgery resulted in numerous subacute and chronic poisonings.

As either a solution or a vapor, phenol penetrates into the skin rapidly. Phenol vapors are also well absorbed by the lung. Although the onset of phenol poisoning can be abrupt, the dangerous phase of the intoxication is usually complete in 24 hours. A profound central nervous system depression with coma, hypothermia, loss of vasoconstriction, cardiac depression, and respiratory arrest are the most common manifestations of systemic phenol poisoning (6). Changes in heartbeat rate, systolic blood pressure, and the activity of blood cholinesterase were reported in workers exposed to phenol vapors for 6 hours with the concentrations of phenol increased from 3 mg/m^3 to 9 mg/m^3 (18). Respiratory death of pulmonary origin, cardiac death, and renal complications were frequently reported (6). In many of the above cases, the original contact with phenol was cutaneous rather than by mouth.

Phenol has recently been used by plastic surgeons for chemical face peeling. Cardiac complications (with tachycardia being the most frequent), were reported by 13% of the plastic surgeons using this procedure (9).

Chronic exposure to phenol has caused brown discoloration of skin and dark pigmentation of ligaments, cartilage, fibrous tissue, skin, and urine (16). Marked corrosion and skin necrosis is produced by 10% solutions of phenol (6). Schmidt and Maibach (17) reported an immediate and delayed dermatitis produced by topical phenol exposure. The immediate painful skin necrotic eruption produced by contact with chemicals containing 10% phenol extends proximally without any further contact with the chemical, leaving skip areas of normal skin. Approximately 3 to 7 months later, spontaneous flares appeared within the area of original contact. Gradual release from an initially formed phenol-protein complex was thought to be responsible for the progression beyond the contact area and the delayed reaction.

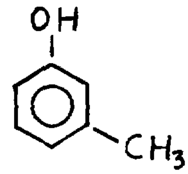
Metabolism. "Phenol is a normal constituent of animal and human tissues and also occurs in the urine, feces, saliva, and sweat. Background levels of phenol arise from microbial metabolic activities, particularly the metabolism of tyrosine and the catabolism of proteins, in the intestines. *Escherichia coli* is thought to be the main producer of phenol. The production of phenol is a function of the type of diet, with a high protein or meat diet promoting phenol formation. The phenol, so formed, may be conjugated with various acids and may be oxidized, either completely to carbon dioxide or incompletely to quinol (1,4-dihydroxybenzene) and catechol (o-dihydroxybenzene). The production of phenol in the body may be elevated by exposure to chemicals that are metabolized to phenol, such as benzene and phenylsalicylate. In addition, pathological conditions that involve the catabolism of body tissues elevate the levels of phenol in the body. A rise in free and conjugated phenol was detected in the blood of human beings afflicted with pernicious anemia, gangrene of the lungs, cirrhosis of the liver, and carcinoma of the stomach" (3).

Patients with chronic renal failure had abnormal function of blood platelets which has been associated with elevated levels of phenol and phenolic acids in serum. In vitro studies showed the inhibition of secondary platelet aggregation by phenol (5). Laboratory studies on binding of phenol and its derivatives to human serum proteins showed that phenol itself was bound least to most proteins as compared to the derivatives (7). A correlation between the toxicity of nitrophenols and their binding property with serum albumin has also been reported (10).

Phenol is now recognized as a general cytoplasmic poison toxic to all cells. However, its metabolic effects are still poorly understood. Gosselin (12) quotes a study showing that a nontoxic dose of ^{14}C-labeled phenol in man was excreted in 24 hours, principally as the sulfate (77%) and as the glucuronide (16%) with small amounts of sulfate and glucuronide conjugates of hydroquinone. He adds that with larger doses, free (unmetabolized) phenol can presumably be found in the urine. In other studies, the content of urine phenol is used for the evaluation of phenol exposure (4, 11,). The evaluations apparently assume that there was no exposure to benzene, since phenol is also the urinary metabolic end product of benzene.

Carcinogenicity. Phenol is a tumor promoter. Its tumor-promoting activity was noted in "S" albino mice pretreated with 9,10-dimethyl-1, 2-benzathracene (DMBA) in acetone followed by weekly skin applications of 20% phenol. Phenol at 5% had only a weak tumor-promoting activity. However, 20% phenol alone (i.e., without prior treatment with DMBA) was weakly carcinogenic; no carcinogenic activity was noted with 5% phenol alone. Although a tumor promoter, phenol is not a cocarcinogen (3). NIOSH (1976), in their recent review of the relevancy of the occupational standard for phenol, has stated that there is no evidence that phenol acts as a specific carcinogen; the one study that did show phenol to have weak carcinogenic properties did not evaluate the effects of the solvent (i.e., acetone) used to dissolve the phenol.

Cresol (Methyl Phenol, Hydroxytoluene) $CH_3C_6H_4OH$



Cresol occurs in three isomeric forms (ortho, meta, and para). Ortho- and meta-cresols are crystalline; para-cresol is liquid. A commercially available mixture of three isomers occurs as a colorless, yellowish, or pinkish liquid wtih a phenolic odor. Cresol isomers are derived from coal tar or petroleum. Cresol is used in making synthetic resins, as a disinfectant, in photographic developers, and in explosives.

Toxicity of cresol is regarded as similar to that of phenol; meta-cresol is less toxic than ortho-cresol, and para-cresol is the most toxic (1, 15).

Toxic effects which develop in 20 to 30 minutes after absorption are headache, dizziness, dimness of vision, tinnitus, irregular and rapid respiration, weak pulse, dyspnea, and profound muscular weakness, with occasional mental confusion. On tissue contact, cresol can be absorbed through the skin and produce local and systemic damages in humans. The skin is considered the primary route of occupational exposure to cresol. Skin contact with cresols has resulted in skin peeling on the hands, facial peripheral neuritis, severe facial burns, and damage to internal organs, including loss of kidney function and necrosis of the liver and kidneys. Sensitization of the skin and dermatitis developed on the fingers of workers who had been using a solution containing cresol and cresylic acid (14). Fatalities can occur from prolonged skin contact (15).

Appreciable concentrations of cresol vapors are rarely generated in industry, because all three cresol isomers have low vapor pressures. However, a hazardous concentration of vapor may be generated at elevated temperatures, and there have been a few reports in the literature describing effects from inhalation of cresol vapor (14). Workers exposed to airborne cresol at an unspecified concentration developed headaches and nausea. Some workers also developed hypertension, muscular irritability, convulsions, and decreased kidney function.

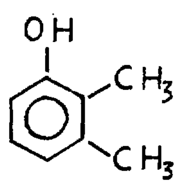
Out of 10 persons exposed to o-cresol vapor at a concentration of 6 mg/m^3, 8 complained of dryness of the respiratory mucosa, nasal constriction, irritation of the throat, and the sensation of an unspecified taste (14).

Several cases of cresol ingestion (mostly as suicidal attempts) have shown cresol to be corrosive to body tissues and to cause toxic effects on the vascular system, liver, kidneys, pancreas. In some cases death has followed. Cresol introduced into the uteri of pregnant women has caused abortion, extensive hemolysis, erosion of blood vessels, damage to the kidney tubules, necrosis of the liver, and death (14). Pathologic description of changes induced by cresol are similar to those caused by phenol.

No investigations of the mutagenic or teratogenic potential of cresol were found. Studies on the role of phenol and its derivatives, including cresol and xylenol, in promoting the formation of both papillomas and carcinomas suggest that the cresol and xylenol isomers may promote the production of benign tumors (14).

Because of the lack of relevant quantitative toxicity data and in view of the closely analogous toxic action to phenol, a TWA of 5 ppm for mixed cresols is recommended by ACGIH (1).

<u>Xylenol (Dimethyl Phenol, Dimethyl Hydroxy Benzene)</u> $(CH_3)_2C_6H_3OH$



There are 6 isomers of xylenol:

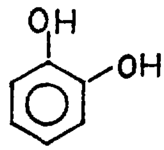
2,3-dimethyl phenol (needles)
2,4-dimethyl phenol (crystals)
2,5-dimethyl phenol (crystals)
2,6-dimethyl phenol (needles)
3,4-dimethyl phenol (needles)
3,5-dimethyl phenol (needles)

Xylenols are used in the preparation of coal tars and disinfectants, and in the manufacture of synthetic resins.

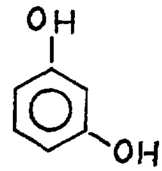
No data on human exposure to xylenols were found.

<u>Dihydroxybenzenes</u> $C_6H_4(OH)_2$

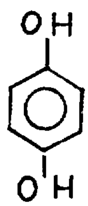
<u>Catechol (1,2-Dihydroxybenzene, 1,2-Benzenediol, Pyrocatechol)</u>



<u>Resorcinol (1,3-Dihydroxybenzene)</u>



<u>Hydroquinone (1,4-Dihydroxybenzene, Quinol)</u>



Dihydroxybenzenes (DHB) are white crystalline compounds with a faint phenolic odor. The greatest use of dihydroxybenzenes, hydroquinone and catechol particularly, is as developers in photography. The second greatest use is in the rubber industry as tire and rubber adhesives. Another use is as antioxidants in rubber and in the food industry. Catechol and resorcinol are also used in fur dyeing and leather tanning.

Except for resorcinol, DHBs are more toxic than phenol. Experimental studies on humans and animals have demonstrated low chronic toxicity and rapid excretion of DHBs. They are absorbed from the gastrointestinal tract and readily absorbed through human skin. After absorption of catechol and hydroquinone, one part of the molecule is oxidized to the more toxic compound, quinone, whereas the other part of the molecule conjugates with hexuronic, sulfuric, and other acids. Resorcinol is excreted in the free state and is conjugated to acids. The symptoms of intoxication by DHBs resemble those induced by phenol poisoning; nausea, dizziness, a sense of suffocation, an increased rate of respiration, vomiting, pallor convulsions, headache, dyspnea, cyanosis, delerium, and coma. Catechol can cause depression of the central nervous system and a rise of blood pressure resulting from peripheral vasoconstriction. Unlike phenol, DHBs do not have a tumor-promoting activity, but catechol is reported to have a co-carcinogenic activity (8).

Cases of dermatitis have resulted from skin contact with hydroquinone, and with other derivatives of phenolic compounds (2). Cases of keratitis and discoloration of the conjunctiva have been reported among men exposed to hydroquinone vapor or dust. Persons with poor visual acuity caused by astigmatism, keratoconus, or preexisting corneal injury should be excluded from repeated unprotected exposure. Hydroquinone induces hyperemia of abdominal organs that are rich in pigments, pathological changes in the liver and kidney, and bronchopneumonia.

Resorcinol may cause irritation to the eyes and induce dermatitis particularly in sensitive individuals. The cutaneous application of resorcinol solution or salves may result in local hyperemia, itching, dermatitis, edema, and the loss of superficial layers of the skin. Resorcinol markedly affects the spleen, and induces tubular injury in the kidney, fatty changes and anemia in the liver, fatty changes in the heart, and edema and emphysema in the lungs (8).

Catechol contact with the skin can cause an eczematous dermatitis. Catechol induces degenerative changes in the tubuli of the kidney characterized by red blood cells and fibrin clots in the lumina.

Average daily concentration of DHB dust should be maintained below the threshold limit value. Operations, e.g., sieving, blending, and packaging, usually require enclosure and local controlled ventilation. Good housekeeping practices and personal contamination control are essential. In the case of hydroquinone, complete eye protection may be useful for short exposure where other controls are not feasible (8).

Catechol and hydroquinone appear as intermediate products of benzene metabolism in man. Morimoto and Wolff (13) studied the effect benzene and its metabolites had on human lymphotcyes cultured in vitro. They found that catechol is a potent compound, which induces sister chromatid exchanges and readily delays cell division, and that hydroquinone is also potent but to a lesser degree than catechol. Benzene itself does not affect sister chromatid exchange and cell kinetics. Thus the benzene toxicity is most likely due to the formation of catechol and hydroquinone. Subsequent studies showed that catechol and hydroquinone can be optimally metabolized to produce reactive species, presumably benzo(semi)quinones, under conditions of lower metabolic activity than those necessary for phenol and benzene (13).

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RAC 21	SYSTEM											EFFECT							
PHENOLS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Phenol C_6H_5OH	X	X	X		X		X		X								X	X	
Cresol $CH_3C_6H_4OH$	X	X	X			X	X	X	X	X	X				?	X	X	X	
Xylenol $(CH_3)_2C_6H_3OH$	No human data found																		
Dihydroxybenzenes $C_6H_4(OH)_2$	X	X	X			X	X	X	X	X	X			X			X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

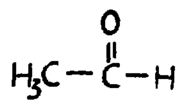
RAC #22 - ALDEHYDES AND KETONES ["CARBONYLS"] (EXCLUDING FORMALDEHYDE)

Aldehydes and ketones are characterized by the presence of the carbonyl group =C=O. Because of the common carbonyl functional group, the properties of aldehydes and ketones are in many ways similar.

Aldehydes listed in RAC #22 include acetaldehyde, acrolein, nonanal, and benzaldehyde; ketones include acetone and acetophenone.

Aldehydes

<u>Acetaldehyde (Ethanal, Ethyl Aldehyde, Acetic Aldehyde)</u> CH_3CHO



Acetaldehyde is a colorless liquid with a pungent fruity odor. It is used in the manufacture of acetic acid and its derivatives, and in other chemical compounds.

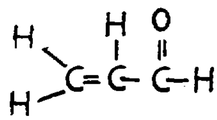
The primary effect of exposure to acetaldehyde in industry is irritation of the eyes and mucous membranes (irritation of the upper respiratory system). Changes in light and auditory sensitivity have also been observed (4).

Some workers reported eye irritation at 50 ppm but acclimatation occurred later. Concentrations of 200 ppm produce eye irritation and transient conjunctivitis in almost every exposed person (1).

In high concentrations, acetaldehyde produces narcotic effects. Bronchitis, albuminuria, fatty liver, and lung edema have been reported as high dose inhalation effects. Paralysis of respiratory muscle leading to death may also result from high dose inhalation (1, 3, 4, 9). Prolonged exposure causes a decrease of red and white blood cells. Prolonged contact with skin produces erythema, burns, and chronic dermatitis. Acetaldehyde increased the frequency of sister chromatid exchange in cultured human lymphocytes (2) and significantly inhibited lymphocyte function (7).

No health hazards of acetaldehyde have been found in industry when recommended standard precautions were followed (3).

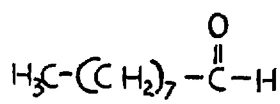
<u>Acrolein (Propenal, Acrylaldehyde)</u> CH_2=CHCHO



Acrolein is a colorless or yellowish liquid with a disagreeable choking odor. It is used as an intermediate for the synthesis of glycerol, resins, pharmaceuticals, herbicides, and as a tear gas. Acrolein is also utilized in protecting liquid fuels against microorganisms.

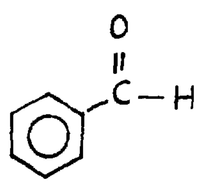
Acrolein is highly irritating to the eyes, nose, and upper respiratory tract. High concentrations can cause pulmonary edema. Exposures of 1 ppm are immediately detectable, 5.5 ppm produce intense irritation, and 10 ppm and over can be lethal in a short time. Contact with liquid acrolein causes severe corneal injury and burns of the skin. Swallowing produces acute gastrointestinal distress, pulmonary congestion and edema (1, 3-7).

<u>Nonanal (n-Nonaldehyde, Pelergonaldehyde)</u> $C_9H_{18}O$



No human health data were found.

<u>Benzaldehyde (Benzencarbonal, Benzencarboxyaldehyde)</u> C_6H_5CHO

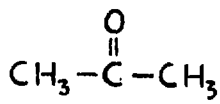


Benzaldehyde is produced by oxidation of toluene as a co-product of benzoic acid. It is used in the food and pharmaceutical industry and in the manufacture of odorants and flavoring chemicals like cinnamaldehyde (3).

Benzaldehyde is nontoxic but its vapors have a mild narcotic effect, causing depression of the central nervous system. High concentrations can cause convulsions. It can be also irritating to eyes, and skin contact can cause dermatitis (4, 9).

Ketones

Acetone (2-Propane) CH_3COCH_3



Acetone is a colorless volatile flammable liquid with an aromatic odor. It is a widely used industrial solvent and chemical intermediate. It is found in paints, varnishes, lacquers, and is used as a solvent for cements in the leather and rubber industries.

Studies on exposures to low concentrations show controversial results. According to ACGIH (1), Nelson et al. reported slight irritation after 3 to 5 minutes' exposure at 300 ppm, whereas DiVincenzo found no effect after 2 to 4 hours' exposure at 500 ppm except for an awareness of odor.

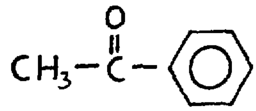
Inhalation of acetone at 500 ppm causes eye, nose, and throat irritation. Higher concentrations (1000 ppm) cause dryness of the mouth and throat, dizziness, nausea, uncoordinated movements, loss of coordinated speech, drowsiness, and, in extreme cases, coma (1, 4, 5).

Direct contact of acetone with skin may cause dermatitis. Acetone readily penetrates the skin, but it is rapidly excreted in urine and breath.

Examination of workers engaged in the production of acetone, where concentrations were reported to be 700 ppm for 3 hours/day for 7 to 15 years, demonstrated chronic inflammation of the respiratory tract, stomach, and duodenum, attacks of giddiness, and loss of strength. Kidney and liver damage were also observed (1, 4).

The recommended TLV is 750 ppm. Recommendations in other countries range from 83 ppm [(Bulgaria, Hungary, Poland (1970)], to 1000 ppm [(Finland and Germany (1976)].

Acetophenone (Acetylbenzene, Methyl Phenyl Ketone, Hypnone) C_8H_8O



Acetophenone is a liquid made from benzene and acetylchloride. It forms laminal crystals at low temperatures. It is used in perfumes (orange-blossom-like odor) as a catalyst for polymerization of olefins, and in organic syntheses.

Acetophenone in high concentrations produces a narcotic effect. It can affect pulse rate and cause a slight but continuous decrease of hemoglobin. Contact with skin produces irritation. Acne-like skin lesions have been reported. Contact with eyes causes transient corneal injury (4, 8).

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RAC 22	SYSTEM											EFFECT							
ALDEHYDES AND KETONES (Excluding Formaldehyde)	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Acetaldehyde CH_3CHO		X	X		X		X	X	X		X						X	X	
Acrolein $CH_2=CHCHO$		X	X			X		X									X		
Nonanol $C_9H_{18}O$	No human data found																		
Benzaldehyde C_6H_5CHO			X					X	X								X	X	
Acetone CH_3COCH_3			X			X	X	X	X		X						X	X	
Acetophenone $C_6H_5COCH_3$	X		X		X				X								X	X	

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

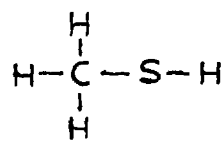
RAC #23 - NONHETEROCYCLIC ORGANO SULFUR

Category #23 includes: 1) thiols and 2) sulfides, disulfides and sulfates.

Thiols

Formerly called mercaptans, thiols are formed from alcohols in which the oxygen in the hydroxyl (OH) group is replaced by sulfur (SH).

Methyl Mercaptan (Methanethiol, Thiomethyl Alcohol, Mercaptomethane, Methyl Sulfhydrate) CH_3SH



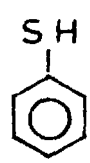
Methyl mercaptan is a flammable, water soluble gas with a disagreeable odor. It is added to natural gas in order to give it odor. It is used in the synthesis of methionine, and as an intermediate in the production of pesticides, fungicides, jet fuel, and plastics. It is a by-product in the operations of paper and pulp mills.

Reported toxicity of methyl mercaptan is similar to that of hydrogen sulfide. It acts on the respiratory center, producing respiratory paralysis leading to death. Less acute concentrations cause pulmonary edema (1).

A worker handling tanks used for holding methyl mercaptan was hospitalized because of coma; acute hemolytic anemia and methemoglobulinemia developed (1).

Contact with liquid methyl mercaptan is painful and irritating to eyes and skin. The exposure to vapors produces loss of sense of smell and loss of consciousness with temporary physiological impairment.

Thiophenol (Phenyl Mercaptan, Mercaptobenzene, Benzenethiol) C_6H_5SH



Thiophenol is a colorless liquid with a repulsive garlic-like odor. It is used as a chemical intermediate, solvent, and mosquito larvicide.

It is a definite skin irritant and should be considered moderately toxic. It can cause severe dermatitis, headaches, and dizziness (1). No human data on subchronic or chronic exposures were found.

Animal data indicate effects of thiophenol on the central nervous system; some changes in kidney, lung, and liver were also observed. It is lethal in higher doses.

Sulfides, Disulfides, and Sulfates

Carbonyl Sulfide (Carbon Oxysulfide) COS

$$O=C=S$$

Carbonyl sulfide is listed as an irritant by Sax. When heated to decomposition, it may liberate hydrogen sulfide fumes. In high concentrations, it may act as a narcotic.

Diethyl Sulfide (2,2-Thiodiethanol, Thiodiethylene Glycol) $(C_2H_5)_2S$

$$CH_3-CH_2-S-CH_2-CH_3$$

No data available.

Carbon Disulfide (Carbon Bisulfide) CS_2

$$S=C=S$$

Carbon disulfide is a clear, colorless, or faintly yellow liquid. Technical grade CS_2 has a strong odor of the hydrogen sulfide with which it is contaminated.

Carbon disulfide is used in the manufacture of viscose rayon, carbon tetrachloride, cellophane films; in rubber and polymer industries; in the preparation of a variety of sulfur compounds; and as a solvent.

Carbon disulfide vapor is absorbed largely through the lung, and toxic quantities can also be absorbed through the skin. The toxic effects are mostly on the nervous system. Single exposures may cause narcosis. Intoxication of workers exposed to carbon disulfide produces psychological and behavioral symptoms. Symptoms start with headache, fatigue, insomnia, rapid changes of mood, and some psychomotor and intellectual impairments. The symptoms can progress to severe emotional and mental disorders and to Parkinson's-like syndromes (1,2,4,12,13,19,22,25,26,31-33,36,42-44). Chronic peripheral neuropathy has been reported in workers with previous exposure to CS_2, thus indicating that carbon disulfide can cause permanent axomal neuropathy (8).

Ocular changes (blind spot enlargement, contraction of peripheral field, corneal anesthesia, impairment of optic nerves, retinopathy) have also been reported (9,17,28,32,34,39,42). Ophthalmoscopic tests indicate microaneurysm, the incidence of which being proportional to the duration and intensity of exposure to carbon disulfide (38).

Exposure to carbon disulfide can accelerate coronary heart disease, hypertension, and atherosclerosis (3,27,32,37,40). Epidemiologic studies of viscose rayon workers indicate a 2.5- to 5-fold increase in risk of death from coronary heart disease as compared with the risk to unexposed workers (2,11,32,41).

However, the tests for total cholesterol, high-density lipoprotein cholesterol, triglycerides, blood pressure, and 2 coronary heart disease risk indices of 70 male viscose rayon workers exposed to CS_2 at 35 mg/m^3 did not differ from 70 individually matched controls (10). The authors conclude that apart from a possible toxic effect directly induced by CS_2 on the myocardium, CS_2 exposure up to 30 mg/m^3 did not promote atherosclerosis nor increase the risk of coronary heart disease. Metabolic ultrastructural changes have been reported in the myocardium after prolonged exposure to low concentrations of carbon disulfide (17).

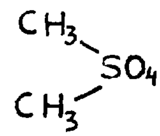
Other reported effects of exposure to carbon disulfide include menstrual disturbances and secretion of carbon disulfide in the mother's milk (5), and a decrease in nonspecific humoral resistance to infectious diseases (18). A community study reported an increased rate of spontaneous abortions in women employed in rayon textile jobs and paper product jobs, as well as in wives of men employed in transport and communication, in rayon textile jobs, and in chemical process jobs (15). Increased adhesiveness of blood platelets reported in workers with mild exposure to carbon disulfide was reported (39A). The platelet adhesiveness can be reduced by the prophylactic treatment of workers with Cynarex (45).

Carbon disulfide alters the metabolism of lipids (13,20,31A) and of carbohydrates resulting in the decrease in glucose tolerance in diabetics (3,6,10,14,16).

The chronic and acute effects of carbon disulfide are ascribed to its high reactivity with nucleophilic cellular components such as amino acids, catecholamines, and steroids. It affects human metabolism by chelate formation with essential metals in enzymic system, and inhibition of vitamin B_6 activity and catecholamine metabolism (3A,7,12). Long-term studies on catecholamine metabolism in viscose spinners exposed to carbon disulfide show that inhalation over 80% of the work time results in increasing excessive excretion of adrenaline, noradrenaline, dopamine, and dopa. The excretion of noradrenaline reached a plateau within 6 to 10 years, and that of remaining catecholamines within 5 years (21). Studies on serum metals show a decrease in the level of Zn associated with an increase in urinary Zn (24) and a decrease in Ca and Mg levels in the blood of exposed workers (29,30).

The levels of blood serotonin and of 5-hydroxyindoloacetic acid in the urine of persons exposed occupationally to CS_2 varied with its concentration and the exposure length. The respective blood and urinary tests were suggested as indicators of CS_2 poisoning (23). Urinary levels of 2-thio-thiazolidine-4-carboxylic acid (TTCA) in workers exposed to the carbon disulfide in a Belgian viscose plant varied among different individuals doing the same jobs and for the same individuals in the course of the working period, with a marked increase during the exposure. The correlation between individual personal monitoring results and the increase in TTCA levels was found to be statistically significant (35).

Dimethyl Sulfate $(CH_3)_2SO_4$



Dimethyl sulfate is a colorless liquid with a faint onion odor. The vapor has no odor and thus has no warning properties. It is used as a methylating agent in the manufacture of many organic chemicals.

Animal studies suggest carcinogenic properties of dimethyl sulfate. Clinical and x-ray evidence suggest possibilities of an excess of lung cancer among workers exposed to dimethyl sulfate, but epidemiologic data are insufficient (1).

Early (before 1962) cases of dimethyl sulfate poisoning in industrial workers reported in Europe describe headache and giddiness with burning of the eyes as primary symptoms reaching a maximum in 2 to 10 hours. The condition becomes progressively worse with painful photophobia, irritation of the respiratory tract, cough, difficulty in breathing and swallowing, vomiting, diarrhea, and burning micturition. Dysuria persists for 3 to 4 days, and congestion of mucous membranes and laryngeal edema may persist for two weeks. Some impairment of liver function and reduction in the visual fields were observed six years later.

Burns of the skin and eyes as the primary acute effects from overexposure to dimethyl sulfate were reported in plants where leakage sites showed close to 0.2 ppm. There was, however, no evidence of excess cancer death (1).

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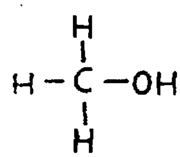
RAC 23 — NONHETEROCYCLIC ORGANO SULFUR	SYSTEM: Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	EFFECT: Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Methylmercaptan CH_3SH		X	X		X			X									X		
Thiophenol C_6H_5SH		?	X				?		X		?						X		
Carbonyl Sulfide COS									X								X	X	
Diethyl Sulfide $(C_2H_5)_2S$		No human data found																	
Carbon Disulfide CS_2	X				X			X	X	X					X		X	X	
Dimethyl Sulfate $(CH_3)_2SO_4$		X				X	X	X	X		?	?					X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #24 - ALCOHOLS

The two compounds covered in this category are methanol and ethanol.

Methanol (CH_3OH)



Methanol is a mobile, highly polar liquid. It is miscible with water, ethyl alcohol, ether, and many other organic solvents (1). Methanol is used as a solvent for nitrocellulose, ethyl cellulose, various natural synthetic resins, and in paint removers. It is also used as a denaturant for ethyl alcohol, as an antifreeze, and in the manufacture of formaldehyde and other chemicals (notably methyl derivatives) (1). Methanol is also found in the exhaust of cars equipped with catalytic converters and in cigarette smoke.

Acute Effects. Exposure to vapor levels of 200 to 500 ppm in a confined space may cause headaches and eye irritation. Exposures of 800 to 1200 ppm and above have caused permanent diminution of vision. The extent of the visual damage depends on the length and amount of exposure. Very high concentrations, especially in a confined space, will cause the same symptomatology as ingestion of methanol.

Ingested, methanol is highly toxic. As little as 2 tsp. can cause symptoms. The fatal dose in man ranges between 2 and 8 ounces (9). The immediate symptom of methanol ingestion is inebriation, indistinguishable from that of ethanol ingestion. This may be followed by an entirely asymptomatic interval. After a latency period of 6 to 30 hours (usually 12 to 18 hours), the characteristic symptoms of methanol toxicity appear. These include: headache; weakness; leg cramps; vertigo; nausea and vomiting sometimes with violent abdominal pain; back and leg pain; vision defects; rapid shallow breathing from metabolic acidosis; and weak rapid pulse with hypotension progressing to apathy and coma, or to excitement, mania, and convulsions. If death occurs, it is usually from respiratory failure. In nonfatal cases, convalescence is often protracted and can be complicated by debility, permanent eye damage (with possible blindness), kidney damage, and motor dysfunctions (7,9). Since ethyl alcohol inhibits the metabolic oxidation of methanol, methanol poisoning is treated by administering ethanol in small quantities every 3 to 4 hours, along with bicarbonate to combat acidosis.

Methanol is readily absorbed through the skin. There have been reports of death, blindness, and other injuries from methanol spilled on clothing or applied to large areas of the skin. Immersing a whole hand in methanol for two minutes results in the absorption of 170 mg (0.2 ml) (7). Gimenez et al. (8), reported cases of 21 children with soaked methanol clothing applied to their bodies as treatment for "colicky abdominal pain" and other "unspecified symptoms." Early toxic symptoms exhibited by these children were central nervous system depression of variable degrees with alternate periods of excitation. Eleven of these children developed tonic-clonic convulsions, 8 developed anuria or severe oliguria, and 12 children died from cardiac and/or respiratory arrest despite aggressive treatment. Post mortem of one case revealed marked edema and softening of the brain (8).

Direct contact with the skin can cause erythema, dermatitis, and scaling (16).

Chronic Effects. Since methanol is slowly eliminated from the body, repeated exposures can result in increasing methanol blood concentrations. Chronic effects from repeated exposures to high levels of methanol vapor include conjunctivitis, diminished vision, giddiness, headaches, insomnia, gastric disturbances, and metabolic acidosis (1).

A TLV of 200 ppm and an STEL of 250 ppm have been set for methanol.

Ethanol (C_2H_5OH)

$$CH_3-CH_2-OH$$

Ethanol is a colorless flammable volatile liquid. It is commonly used as a solvent and in the manufacture of denatured alcohol, and as a raw material in plastics, lacquers, polishes, plasticizers, perfumes, and cosmetics. In diluted form it is used in alcoholic beverages and in medications.

Acute Effects. Inhalation of 1000 ppm causes slight mucous membrane irritation and lightheadedness. Exposures of 5,000 to 10,000 ppm cause stupor, sleepiness, headache, irritation of the eyes and mucous membrane of the upper respiratory tract, and a sensation of warmth (1,13). Intoxication from inhalation of ethanol vapors is possible, but rare.

Ingested, ethanol is a central nervous system depressant causing various states of inebriation, and possibly coma and death, depending upon amounts ingested. A blood concentration of 0.3 to 0.4% is associated with stupor or coma and 0.5% blood concentration can be fatal (9). Severe hypoglycemia often follows a bout of heavy drinking (13).

Splash contact with the eye causes immediate stinging and burning with reflex closure of the lids and tearing, transitory injury of the corneal epithelium, and hyperemia of the conjunctiva. A foreign-body-type discomfort may be felt for one or two days, but healing is usually rapid and complete.

Ethanol can be absorbed through the skin. A case of ethanol intoxication was reported in a 15-day-old infant treated with dressings containing alcohol (5). No cases of adult intoxication via percutaneous absorption were found.

Ethanol ingestion has been clearly implicated as a major factor in the induction of trauma.

Chronic Effects. Since ethanol is metabolized by the liver, chronic exposure to ethanol causes liver impairment. Cirrhosis of the liver is a common finding among persons with a history of chronic alcoholism. Persons exposed to ethanol (via ingestion or possibly via inhalation) are also more susceptible to the toxic effects of other compounds which are hepatotoxic, such as volatile organochlorines.

Hypertension is a clinical feature often found in heavy alcohol drinkers (4,17). A higher-than-normal incidence of cerebral blood vessel spasms, cardiac depression, arrhythmias, cardiomyopathy, and sudden death has been observed in persons who are "binge drinkers" (2,3). Alcoholic consumption will also decrease cerebral blood flow and increase susceptibility to cerebral thrombosis (15A).

Hillbom et al. (11), found decreased fibrinolytic activity, increased factor VIII complex, and shortened bleeding time in a group of healthy volunteers who were given ETOH. The highest levels of these factors were detected 16 hours after ingestion.

On the basis of animal experimentation, Kaufman et al. (12), have suggested that ethanol consumption at the time of conception may be the cause of certain types of chromosomal defects commonly observed in human spontaneous abortions. Alcohol consumption by women during pregnancy has been reported to cause an increased incidence of first and second trimester abortions, an increased risk of placenta abruptio (1,14), an increased incidence of low birth weights and stillbirths, and an increased risk of birth and developmental defects (10). In addition, offspring of pregnant women who drink during pregnancy (averages of 1 to 2 ounces daily) have a higher incidence of clinical features of abnormal growth (7). Ouellette et al. report a 32% incidence of congenital abnormalities in offspring of women who are heavy drinkers (average of 174 ml absolute alcohol/day), and a 14% incidence of abnormalities in offspring of women who are moderate drinkers (6). Fetal alcohol syndrome is an entity commonly seen in infants born to alcoholic mothers. These infants experience alcohol withdrawal symptoms and often suffer permanent brain damage.

Chronic drinking in men has been associated with testicular atrophy, azoospermia, and testicular pathology (7).

Degenerative changes have been found in myelinated and unmyelinated fibers in alcoholics (15A).

A TLV of 1,000 ppm has been set for ethyl alcohol.

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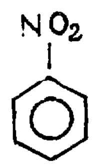
RAC 24	SYSTEM											EFFECT							
ALCOHOLS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Methanol CH_3OH	X	X	X			X	X	X	X								X		
Ethanol C_2H_5OH	X				X			X	X	X	X		X	?	X		X	X	

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

Aromatic nitro compounds contain a nitro ($-NO_2$) substituent on the ring.

Monocyclic Nitroaromatics

<u>Nitrobenzene</u> $C_6H_5NO_2$



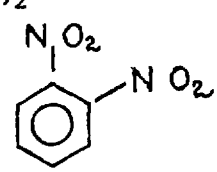
Nitrobenzene is a colorless-to-pale-yellow oily liquid, with an odor resembling bitter almonds. It is used in the manufacture of aniline and benzidine, in soaps, shoe and metal polishes, and as a solvent.

Nitrobenzene is a highly toxic substance readily absorbed by contact with the skin and by inhalation. Workers exposed for 8 hours to 1 ppm nitrobenzene in the air would absorb 25 mg of nitrobenzene of which, one third would be by skin absorption. The primary effect of nitrobenzene toxicity is the conversion of hemoglobin to methemoglobin, and the appearance of cyanosis when the methemoglobin level reaches 15%. Nitrobenzene affects the central nervous system and produces fatigue, headache, vertigo, vomiting, general weakness, and, in some cases, unconsciousness and coma. The usual latent period before appearance of symptoms is 1 to 4 hours.

Chronic exposure can lead to spleen and liver damage, jaundice, anemia, and methemoglobinemia (1,7). Both the cyanogenic and anemiogenic potentials of nitrobenzene are listed as considerably greater than those of aniline.

Nitrobenzene was included in a list of 14 aromatic nitro compounds suspected of carcinogenic activity (4).

<u>Dinitrobenzene</u> (DNB) $C_6H_4(NO_2)_2$

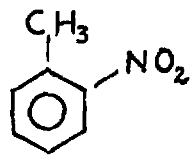


Dinitrobenzene occurs in three isomeric forms (ortho, meta, and para) as white (ortho and para) or yellow (meta) crystals. DNB is used in the manufacture of dyes, as a camphor substitute, in the production of celluloids, and in organic syntheses.

Dinitrobenzene is a higly toxic substance producing methemoglobinemia. Prolonged exposure may lead to liver damage (1).

Dinitro aromatic derivatives are at least five times more toxic than the corresponding mononitro compounds.

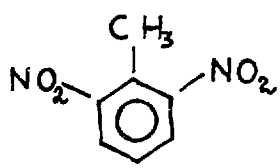
<u>Nitrotoluene</u> $CH_3C_6H_4NO_2$



Nitrotoluene occurs in three isomeric forms. Ortho- and meta-nitrotoluenes are liquids; the para isomer is a yellowish crystalline. All isomers are used in the manufacture of other chemicals such as toluidine, fuchsin, tolidine, and various dyes.

Nitrotoluene has a low toxicity, especially when compared with nitrobenzene. Poisoning from nitrotoluene is uncommon (1).

<u>Dinitrotoluene</u> (2,4-Dinitrotoluene; DNT) $CH_3C_6H_3(NO_2)_2$



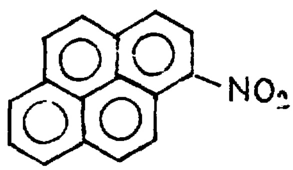
Commercial DNT is a combustible, oily liquid, composed of a mixture of ortho, meta, and para isomers. The pure isomers are yellow crystals. DNT is used in the manufacture of explosives and dyes, and in organic synthesis.

The toxic effect of DNT is similar to that of other aromatic nitro compounds. The first and most characteristic symptom is methemoglobinemia. Animal experiments suggest that DNT is less acutely toxic than dinitrobenzene. According to Gosselin (2), liver injury may be more common than cyanosis, especially if the diet is deficient in protein. Of several isomeric forms of DNT, the 2,4-dinitrotoluene is more toxic for animals than other DNT isomers. The cyanogenic potential of DNTs is evaluated below that of aniline, but their anemiagenic potential is considered greater (1).

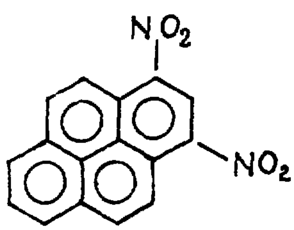
Studies of the metabolism of 2,4-dinitrotoluene by intestinal microorganisms from rat, mouse, and man showed that an ordered sequence of reductive metabolism occurs under anaerobic conditions. The 2- and 4-nitro groups were reduced to amino groups (3). The test on _Salmonella typhimurium_ showed the mutagenic activity of DNT enhanced by a para orientation of nitro groups (11).

Polycyclic Nitroaromatics

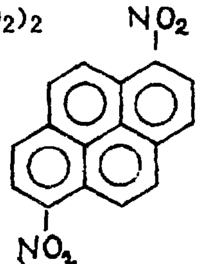
1-Nitropyrene (3-Nitropyrene) $C_{16}H_9NO_2$



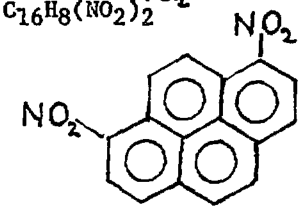
1,3-Dinitropyrene $C_{16}H_8(NO_2)_2$



1,6-Dinitropyrene $C_{16}H_8(NO_2)_2$



1,8-Dinitropyrene $C_{16}H_8(NO_2)_2$



Mutagenic activity of 1-nitropyrene has been recognized by tests on Salmonella typhimurium (5,6,10). Mutagenicity of di- and trinitropyrenes tested in cultured hamster ovary cells showed that while 1-NP and 1,3-DNP had only marginal direct-acting mutagenicity, 1,6-DNP, 1,8-DNP, and 1,3,6-TNP showed definite mutagenicity (8). The authors concluded that the positive mutagenic response of the nitropyrenes suggests that they are potentially carcinogenic, and that further research into their possible human health risk should be performed.

The study on the acute and genetic toxicity of 1-nitropyrene in rats showed that the oral dose of 5.0 g/kg did not produce histologic alterations in major internal organs. About 70% of the dose was recovered in feces as nitropyrene (NP) and about 2% was present as the reduced metabolite 1-aminopyrene (AP). Both NP and AP showed low mutagenicity in Chinese hamster ovary cells in vitro. The authors concluded that the evidence of reductive metabolism of NP in rats raises concern about the potential exposure of humans to this compound. However, the weak in vivo and in vitro genetic toxicity of NP at high dose levels in mammalian systems suggests that the potential hazard may not be as high as predicted from bacterial mutagenicity data (9).

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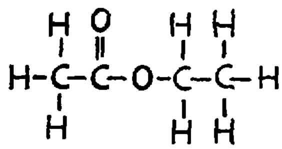
RAC 25	SYSTEM											EFFECT							
NITROAROMATICS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Nitrobenzene $C_6H_5NO_2$					X	X			X	X	X	?							
Dinitrobenzene $C_6H_4(NO_2)_2$					X						X								
Nitrotoluene $CH_3C_6H_4NO_2$																			
Dinitrotoluene $CH_3C_6H_3(NO_2)_2$					X						?								
Nitropyrene $C_{16}H_9NO_2$														X					
Dinitropyrene $C_{16}H_8(NO_2)_2$														X					

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

Ethyl Acetate (Ethyl Ester Acetic Acid) $CH_3COOC_2H_5$



Ethyl acetate is the only ester listed as a synthetic fuel product. Ethyl acetate is a colorless liquid with a fragrant, fruity odor. It is highly flammable and a dangerous fire and explosion hazard.

Ethyl acetate is used as a solvent for varnishes, aeroplane dopes, lacquers, and nitrocellulose, in artificial fruit essences, and in the manufacture of artificial silk and leather, perfumes, and photographic films.

Ethyl acetate has been widely used as a lacquer solvent and has the reputation of being one of the less toxic of the volatile organic solvents. According to Patty, workers exposed regularly at concentrations ranging from 375 to 1500 ppm for several months showed no unusual signs or symptoms. There was, however, a report of the death of a tank painter ascribed to inhalation of ethyl acetate. There have also been reports of poisoning due to inhalation of ethyl acetate (1).

Animals can withstand a daily 4-hour exposure of ethyl acetate to 2000 ppm for a period of 65 days, without apparent ill effects. Ethyl acetate is only mildly narcotic even at concentrations well in excess of 46,000 mg/m^3 (1). Short exposures of 8,600 to 20,000 ppm have been considered dangerous to man. The vapors can be irritating to mucous membranes but provide good warning, since irritation occurs at approximately 400 ppm. Repeated or prolonged direct skin contact will cause drying and cracking of the skin. The threshold limit value (1) is 400 ppm (1.4 mg/m^3). Appropriate ventilation should be used to maintain the concentration of vapor in the air below the TLV. Repeated or prolonged contact with the skin should be avoided (2).

Study of the toxic activity of different industrial solvents on the human lymphocytes cultured _in vitro_ showed that ethyl acetate belonged to the group of compounds which inhibited [3H] thymidine uptake in the absence of the metabolizing system (S9 mix) but have no effect on cell viability (3). These chemicals were considered by authors to be cytotoxic, but their action was not immediately followed by cellular death.

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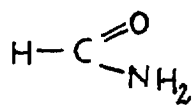
RAC 26	SYSTEM											EFFECT							
ESTERS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Ethyl Acetate $CH_3COOC_2H_5$			X					X	X								X	X	

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #27 - AMIDES

Amides are derivatives of carboxylic acid compounds in which the -OH of the carboxylic acid is replaced by $-NH_2$.

Formamide (Formic Acid Amide; Methaneamide; Carbamaldehyde) $HCONH_2$

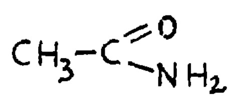


Formamide is a clear viscous liquid used as a solvent in the chemical industry, and as a softener for paper and animal glues.

All toxicology data found about formamide are based on animal studies. It is relatively nontoxic by skin absorption, produces only mild eye irritation, and shows low inhalation toxicity. Teratogenic effects were produced in pregnant rats after injection of formamide (1,3). No human data have been found.

Because of the teratogenic effects found in animals, pregnant women should not be employed in the production and processing of formamide (3).

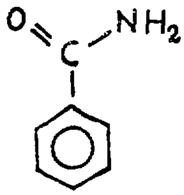
Acetamide (Ethanamide; Acetic Acid Amide) CH_3CONH_2



Acetamide appears as colorless deliquescent hexagonal crystals, odorless when pure. It is used as a solvent, solubilizer, plasticizer, and stabilizer.

Acetamide is a mild irritant (5) for animals, and causes readily reversible tissue changes which disappear after exposure. In high doses, it may act as a carcinogen (2). No human data were found.

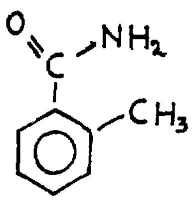
Benzamide (Benzoic Acid Amide; Benzoylamide) $C_6H_5CONH_2$



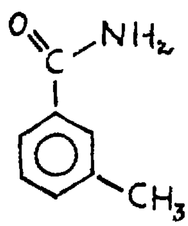
Benzamide forms crystals. No human data were found.

Methyl Benzamide (Methyl Benzoic Acid Amide) $C_6H_4CH_3CONH_2$ appears as isomers.

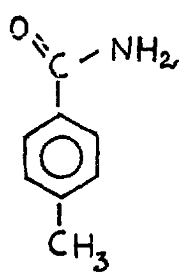
2-Methyl Benzamide



3-Methyl Benzamide



4-Methyl Benzamide



No human data have been found.

Thioacetamide (Ethanethioamide) CH_3CH_2NS

$$CH_3-CH_2-NS$$

Thioacetamide appears as crystals with a slight odor of mercaptan (thiols). Because of its more acceptable odor, thioacetamide represents a pleasant substitute for hydrogen sulfide in the laboratory (4).

No human data were found.

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RAC 27	SYSTEM											EFFECT							
AMIDES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Formamide $HCONH_2$			X					X					?				X		
Acetamide CH_3CONH_2												?					X		
Benzamide $C_6H_5CONH_2$		No human data found																	
Methyl Benzamide $C_6H_4CH_3CONH_2$		No human data found																	
Thioacetamide CH_3CH_2NS		No human data found																	

X = known human effect

? = based on animal data, experience with similar compounds, or inconclusive human data

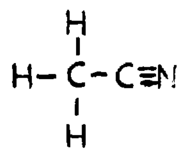
RAC #28 - NITRILES

Nitriles are aliphatic or aromatic cyano compounds with the general formula RC≡N. Most cyano compounds have a characteristic almond-like odor.

Aliphatic Nitriles

Aliphatic nitriles are colorless liquids with faint sweet odors.

Acetonitrile (Acetic Acid Nitrile, Ethane Nitrile, Ethyl Nitrile, Methyl Cyanide, Cyanomethane, Methane Carbonitrile) CH_3CN



Acetonitrile is used as a solvent in the extraction of hydrocarbons and fatty acids, in spectrophotometry and electrochemistry, and as a catalyst and intermediate.

Severe toxic symptoms were reported in a case of 15 painters exposed to acetonitrile vapor for 12 hours in a poorly ventilated tank. The symptoms ranged from nausea, headache, vomiting, respiratory depression, extreme weakness, and stupor to convulsions, shock, and coma. One worker died 14 hours after cessation of exposure. The autopsy showed high cyanide concentrations in the blood, and in various organs. A later analysis of the same case led, however, to the conclusion that the 3- to 12-hr delay in symptoms indicated that the symptoms could not have resulted from cyanide poisoning, and that they resulted from thiocyanate, the detoxification product of cyanide, rather than acetonitrile toxicity (9).

Experimental studies on humans show that inhalation of 40 ppm for 4 hours produced tightness of the chest. Exposures of 160 ppm caused flushing of the face and tightness of the chest, but did not produce significant changes in blood cyanide and urinary thiocyanide concentrations (1,8,9,13).

Although acetonitrile has a low-order toxicity by ingestion, inhalation, and skin absorption, if splashed in the eye it can cause severe eye burns.

<u>Acrylonitrile (Vinyl Cyanide; Propenenitrile; Propenic Acid Nitrile)</u>
CH_2=CH-CN

$$CH_2{=}CH{-}C{\equiv}N$$

Acrylonitrile is used as a monomer for acrylic and modacrylic fibers.

Acrylonitrile is highly toxic by ingestion, inhalation, or absorption through the skin. The toxic symptoms resemble that of cyanide poisoning. It was thus considered that the toxic action of acrylonitrile was due to the liberation of cyanide ion. Although this is a possible secondary mechanism, there is now considerable evidence that the toxic action of acrylonitrile is due to its own structure, independent of the liberation of the cyanide ion (8).

Preliminary epidemiologic studies conducted by chemical companies of a cohort of 470 acrylonitrile polymerization workers indicated excess lung and colon cancer (1,3). The excess of stomach and lung cancer (10) was also reported from the United Kingdom acrylonitrile polymerization workers (17). The epidemiologic studies coincide with experiments on animals indicating carcinogenic action of acrylonitrile (1,14).

The blood serum of workers employed in acrylonitrile production was reported to show a decrease in free sulfur-containing mostly essential amino acids, free sulfhydryl groups, and the diminution of the activity of blood enzymes. The supply of a diet rich in amino acids affected positively the content of free amino acids and the activity of serum enzymes (16). The excretion of acrylonitrile in the urine of exposed workers shows a concentration peak at the end of the workday and a rapid decrease until the beginning of the next workday. A similar increase of acrylonitrile excretion has been observed in non-exposed workers who smoked (levels increased as the number of cigarettes smoked increased), but the concentration of acrylonitrile was much higher in the urine of exposed workers (6).

Several cases of mild jaundice accompanied by mild anemia and leucocytosis have been reported. Other symptoms of prolonged exposure to acrylonitrile include chronic fatigue, respiratory difficulty, and nervous symptoms (7).

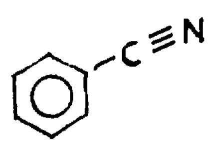
Prolonged skin contact with acrylonitrile causes formation of large vesicles after a latent period of 2 hours. They resemble second degree burns. Repeated skin exposure causes dermatitis.

Experiments testing the mutagenic effect of vinylic monomers on Salmonella showed the mutagenic activity of acrylonitrile (12). The mutagenic activity was enhanced by glutathione, thus supporting the hypothesis of a (liver mediated) formation of a mutagen involving glutathione (4). An increase in sister chromatid exchange and the unscheduled synthesis of DNA in human lymphocytes <u>in vitro</u> were also induced by acrylonitrile (11). Studies on the interaction of acrylonitrile with hepatic microsomes showed the binding of acrylonitrile to human and rat but not to mouse microsomes (2). The basic metabolic pathway of labeled acrylonitrile to 2-cyanoethylene oxide was established <u>in vitro</u>, using subcellular fraction from rats and humans (5). This study also showed irreversible binding of radioactive label from acrylonitrile to protein and DNA.

No significant increase in cytogenic aberration in bone marrow of rat and mouse was recognized in mice given 7 to 21 mg/kg/day of acrylonitrile orally or 10 to 20 mg/kg/day introperitoneally for 30 days, or in rats given 40 mg/kg/day orally for the same period (15).

Aromatic Nitriles

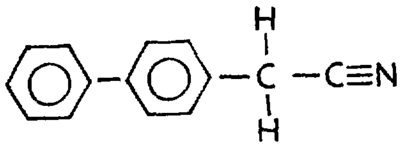
<u>Benzonitrile (Benzoic Acid Nitrile, Cyanobnenzene, Phenyl Cyanide)</u>
C_6H_5CN



Benzonitrile is a liquid with an almond-like odor. It is used as a solvent.

No human data were found.

Diphenyl Acetonitrile (Nitrile Diphenyl Acetic Acid; -Cytanodiphenyl Methane) $C_{12}H_9CH_2CN$.



Diphenyl acetonitrile is a solid at room temperature.

No human data were found.

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RAC 28	SYSTEM											EFFECT							
NITRILES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Acetonitrile CH_3CN		X	X		X	X		X	X								X	X	
Acrylonitrile $CH_2=CH-CN$		X	X		X	X		X			X	X		X					
Benzonitrile C_6H_5CN	No human data found																		
Diphenyl Acetonitrile $C_{12}H_9CH_2CN$	No human data found																		

X = known human effect

? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #29 - TARS

Tars are viscous, bituminous liquids obtained by destructive distillation of organic material. As such, they are mixtures of various chemical categories classified elsewhere in the RAC structure. The mix varies. Unfiltered cigarette tars contain 0.10 to 0.15 µg benzo[a]pyrene, 0.2 to 0.3 µg of pyrene, and 0.25 µg chrysene 1. The following compounds have been identified in coal gassifier tar 2: (1,2)

Dimethylnaphthalene
Acenaphthene
Trimethylnaphthalene
Fluorene
Methylfluorene
Dibenzothiophene
Phenathrene
Anthracene
Methyldibenzothiophene
Methylphenanthrene
Dimethylphenanthrene
Fluoranthene
Pyrene
Phenylnaphthalene
Methylpyrene
Trimethylphenanthrene
Benzo(a)fluorene
Benzo[a]pyrene

No dose-response functions were developed for "tars" (1,2). Exposures to some of these compounds are treated within other RACs.

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RAC 29	SYSTEM											EFFECT							
TARS	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Tars		X	X				X					X				X	X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #30 - RESPIRABLE PARTICLES

Respirable particles are composed of a wide variety of organic and inorganic compounds. They result from direct emission of small particles into the air and from atmospheric chemical reactions of released gases.

A number of epidemiological studies have shown associations between airborne total particle levels and human health (1,2). Dose-response indices have been developed from such studies. Fewer studies, however, have included measurements of respirable particles, and dose-response functions are not available. Moreover, all these studies are based on exposure to particles in general urban air. The character of particles emitted by synthetic fuels plants may be much different.

The chemical constituents of particles are included in other RACs. Rather than develop dose-response functions for respirable particles per se, effects will be estimated on the basis of exposure to specific compounds. In some cases, a compound might be in either gaseous or particulate state. Health impact may depend on which state exposure takes place.

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RAC 30	SYSTEM											EFFECT							
RESPIRABLE PARTICLES	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Respirable Particles	Included in other RACs																		

X = known human effect

? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #31 - ARSENIC

Arsenic, commercially produced as a by-product during the processing of nonferrous metal ores, is principally used in the production of agricultural pesticides, as an additive in metallurgic applications and glass production, as a catalyst in several manufacturing processes, and in medicine. Public exposure to arsenic currently occurs from air, food, and drinking water. The ICRP (4) estimates that the human intake from food and fluids and from inhalation is approximately 1.0 and 0.0014 mg/day, respectively. Marine and freshwater fish and invertebrates appear to be the largest source of arsenic exposure in the diet. Most inhaled arsenic occurs in industrial areas, or in areas where coal is burned; background air concentrations in these regions may range from 1 to 83 ng/m^3, with an average of 3 ng/m^3.

The ACGIH TLV for arsenic has been set at 0.2 mg/m^3, while the OSHA standard is 10 μg/m^3. The US EPA is considering setting drinking water quality standards ranging from 0.0002 to 0.02 μg/l. Similarly, EPA is in the process of developing a National Ambient Air Quality Standard for this pollutant. Acute and chronic health effects of arsenic have been reviewed by a large number of authors. This synopsis draws heavily on the work of Mushak et al. (6), Green (3), U.S. EPA (15), Dickerson (2), and the U.S. National Academy of Sciences (16).

Acute Effects

The main route of entry for nonoccupationally exposed individuals is by ingestion. Typical symptoms of acute oral arsenical poisoning appear within a few hours and include a burning sensation along the gastrointestinal system, nausea, vomiting, diarrhea, cramping, and cardiovascular alterations. Death from circulatory failure may occur within hours or days of an acute lethal dose to trivalent arsenic reported to range from 70 to 80 mg. In less severe poisonings, there may be a delay period of 10 to 21 days before peripheral neuropathy develops. This is reflected by a number of symptoms including weakness, paresthesia, and sensory loss.

Chronic Effects

Effects of chronic arsenic exposure are principally known from occupational studies. Chronic arsenic poisoning through inhalation or ingestion may manifest itself in many different ways.

Neurological disorders are often the most apparent consequence of chronic arsenic exposure. Usually, the sensory pathways are most affected, with overall neuropathy being described as insidious in onset. Polyneuritis, par- and hyper-esthesias, and symmetrical muscle weakness, primarily in distal muscle groups of the lower extremities are common complaints. Central nervous system effects may also occur. These disturbances closely follow peripheral events with symptoms ranging from memory loss and general mental confusion to convulsions, stupor, coma, and even death.

Significant cardiovascular effects have also been observed. Studies of copper smelter workers suggest that their cardiovascular disease mortality incidence rate was twice that of a control population (1). Similarly, vascular changes have been observed in vine dressers who had been exposed to arsenical insecticides for 20 years: vessels in the limbs of these workers had begun to atrophy and became blocked (6).

Documented blood abnormalities include leukopenia (low white cell counts) and anemia. The presence of porphyrin, hemoglobin precursor in the urine, is characteristic of chronic arsenic poisoning. Pathologies affecting the blood do not appear to be permanent, and it has been observed that the blood system usually returns to normal several weeks after exposures cease.

Teratogenic effects of arsenic compounds have been demonstrated in a number of animal studies. Extrapolation of these findings to analogous effects in man is, however, highly speculative. Human epidemiological evidence for teratogenic effects is limited. Increased evidence of spontaneous abortions, infant congenital malformations, and decreased birth weights have been reported for women in populations exposed to relatively high levels of airborne arsenic (7,8). In this population, confounding exposures to other toxic pollutants make it difficult to ascribe the observed effects specifically to arsenic with any degree of confidence.

Carcinogenic effects of arsenic have been seen among occupationally exposed individuals. The strongest links between arsenic and carcinogenesis exist for skin and lung cancers. Associations with other forms of cancer (i.e., liver, hemangiosarcoma, lymphomas, leukemia, renal adenocarcinomas, and nasopharyngeal carcinoma) have also been suggested. Recent epidemiologic studies (5,9,10) have been used by the Carcinogen Assessment Group (14) to derive a dose-response function for respiratory exposure to arsenic. The dose-response relationship is 2.8 respiratory cancers per year per 100,000 persons exposed per $\mu g/m^3$. Ingestion of arsenic compounds has also been associated with an increased risk of skin cancer. Tseng et al. (12) and Tseng (13) studied a limited area in southwestern Taiwan where artesian well water had extremely high concentrations of arsenic; the prevalence of skin cancer for the area was 10.6 per 100. The EPA has established skin cancer risks given arsenic concentrations in drinking water from Tseng's data. A skin cancer risk of 1 per 100,000 is related to water arsenic concentrations of 0.02 $\mu g/l$ (11). These risk levels were calculated by applying a modified "one-hit" extrapolation model to the human epidemiologic data. Because the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. The resulting skin cancer risk is 5.9 cancers per 100,000 persons per $\mu g/l$ arsenic.

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RAC 31	SYSTEM											EFFECT							
ARSENIC	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Arsenic As	X	X	X	X	X	X	?	?	X	X	X	X	?				X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #32 - MERCURY

Mercury is a heavy metal whose toxic effects have been recognized since ancient times. Chronic mercury poisoning was well described in connection with mercury mining in Roman times (3). Although occupational mercurialism has become rare with regulation of mercury levels in today's work environments, epidemics of mercury poisoning have nevertheless occurred in recent years. In the 1950s, industrial discharge of alkyl mercury led to the poisoning of many people who consumed fish and shellfish from the Minimata Bay region of Japan. In the early 1970s, misuse of mercury-treated seed grain led to an outbreak of methyl mercury poisoning in Iraq.

Mercury is currently used in electrical apparatus cells for caustic soda and chlorine production; instruments such as thermometers; laboratory applications; antifouling paint; and dental amalgams (5). Mercury is present in fossil fuels, particularly in crude oil and natural gas deposits located near mecuric sulfide ore (cinnabar). Up to 21 ppm mercury has been found in oil fields. Mercury concentrations in coal are low, but because of the vast quantities consumed annually, coal forms an important source of mercury released into the biosphere (4).

Sources of human mercury exposure are air, water, and food. An ambient air concentration of 50 ng/m^3 is estimated to give an average daily intake of about 1 μg/day (d) by inhalation, but in heavily polluted areas this could increase to 30 μg/d (4). Drinking water, with a mercury level of 50 ng/l, is estimated to contribute 0.1 μg/d to total intake, assuming a consumption of 2 l/d. In the general population, intake of mercury from food is estimated to be between 1 μg/d and 20 μg/d of, which foods other than fish contribute about 5 μg/d. Heavy fish eaters may ingest up to 200 g/d or more (4).

Occupational exposure is generally to inorganic mercury by the inhalation of elemental mercury vapor or to aerosols of mercuric salts (3). For this reason, inhalation exposure to mercury vapor is the major concern of this RAC. However, other forms of mercury will be discussed. The TLV for mercury vapor is 0.05 mg/m^3 and the STEL is 0.15 mg/m^3.

Acute Effects

Mercury vapor is absorbed readily and almost completely across the alveolar membranes of the lung. Inhalation of high concentrations of mercury vapor even for relatively brief periods can cause pneumonitis, bronchitis, chest pains, dyspnea, and coughing, as well as stomatitis, gingivitis, salivation, and diarrhea (1). Kidney damage with renal shutdown may occur within 1 to 2 days (2), and death may occur within a week (6). In contrast to chronic mercury poisoning, mental and nervous symptoms are not common in acute mercurialism, although tremors have been described (4).

Chronic Effects

The critical organ affected by repeated or prolonged exposure to mercury vapor at low levels is the brain.

Chronic mercurialism is characterized by three features: inflammation of the mouth, muscle tremors, and psychic irritability (3). Mouth changes include excessive flow of saliva, metallic taste, soft and spongy gums, and loose teeth. Muscular tremors usually come on slowly and first affect the muscles of the eyelids, tongue, and fingers. Later, tremors spread to the arms and legs; walking becomes difficult and handwriting is changed to a jerky scrawl so characteristic that periodic recording of handwriting is used to detect early evidence of chronic mercury poisoning. Psychic irritability or erethism is a mental disturbance characterized by an apprehensive timidity, shrinking from observation, sense of discouragement, loss of self-confidence; overreaction to criticism, loss of memory, and abnormal sleep patterns (3,4).

Diagnosis of chronic mercury poisoning is not easy because of the nonspecificity of symptoms at low levels. Workers exposed to low concentrations of mercury vapor as a group show a linear relationship between urine mercury levels and the time-weighted average concentration to which they were exposed. However, a consistent relationship was not seen until after one year of exposure. Blood mercury levels are indicative only of recent exposure, since this metal is cleared rapidly from the blood. However, mercury may persist in the blood stream long enough to cross blood-brain and placental barriers (3).

Other Forms of Mercury

All forms of mercury are poisonous if absorbed (7). Mercury toxicity depends on a single basic mechanism: the mercuric ion acts to precipitate protein and to inhibit enzymes containing sulfhydryl groups (3). Exposure to mercuric salts, phenyl mercuric and methoxy methyl mercuric compounds, whether by inhalation or ingestion, leads to kidney damage (4). Methyl mercury and other short-chain alkyl-mercury compounds are virulent neurotoxins upon either acute or chronic exposure and are especially hazardous because of their ability to rapidly penetrate the blood-brain barrier and the placenta (1,7). Fetal methyl mercury poisoning (manifested by microcephaly and cellular changes in the brain) has been reported by mothers showing no clinical evidence of poisoning (4). The relationships between intake of methyl mercury and concentrations in blood and hair have been studied in populations which have ingested methyl mercury-contaminated fish in Japan and contaminated bread in Iraq (4). The effects of methyl mercury have been found to be critically dependent on the dose, that is, the dose-response curve appears to be very steep (7). However, the amount of mercury needed to produce disease is not known and there is no specific biochemical test for a diagnostic aid (5).

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RAC 32	SYSTEM											EFFECT							
MERCURY	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Mercury Hg		X		X		X	X	X	X				X		X		X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #33 - NICKEL

Nickel is a metallic element used in making high temperature and corrosion-resistant alloys (e.g., stainless steel) for numerous end-use products and in multiple industries, including welding, electroplating, products of catalysts, and storage batteries. Nickel occurs in nature primarily as either oxide (laterite) or sulfide ore.

Water-insoluble nickel compounds include the oxides, NiO, Ni_2O_3, carbonate, and sulfide. Trinickel disulfide (Ni_3S_2) is encountered in the refining of certain nickel ores. Soluble salts of nickel include chloride, sulfate, and nitrate.

The general population comes in contact with nickel through air, water, foodstuffs, soil, artifacts such as coins, nickel-plated jewelry, utensils, and cigarettes (two packs of cigarettes contain 3 to 15 μg of nickel). Daily dietary intake of nickel averages 165 to 500 μg. Concentrations in water range from 0.4 to 5.1 μg/l. Air concentrations range from 0.002 to 0.008 $\mu g/m^3$ in nonurban air and an average of 0.021 $\mu g/m^3$ in urban air. Concentrations in soil vary from 5 to 5000 ppm (4). Normal body serum concentration of nickel is 0.8 to 4.2 μg/l (5).

Acute Effects

Documented health effects from nickel or nickel compounds are the results of airborne inhalation. The toxicity level of nickel through oral intake is low, since there appears to be a mechanism in mammals that limits intestinal absorption of nickel (2). Symptoms of nickel toxicity from ingestion are mainly gastrointestinal irritation.

There are scattered reports of patients on kidney dialysis developing hypernickelemia, thought to be due to nickel leaching out of the nickel-plated stainless steel water heater tanks used in dialysis. Symptoms, which include nausea, vomiting, headaches, and palpitations, usually resolve 3 to 13 hours after the dialysis. There have also been reports of patients who have developed dermatitis or allergic asthma after implantation of a nickel-containing prostheses (5).

Albumin and amino acids bind readily to nickel and therefore nickel may be a contaminant in intravenous solutions. Up to 235 μg of nickel may be contained in a liter of albumin solution. Since nickel may increase coronary artery resistance and can have an oxytocic effect on the uterus, it could have adverse effects on patients with acute myocardial infarctions and on pregnant women (5).

Nickel carbonyl [$Ni(CO)_4$], formed by the reaction of carbon monoxide with finely divided nickel is the only nickel compound known to have acute toxic effects. However, studies have not indicated whether nickel, carbon monoxide, or the combination is the primary cause of these effects. Exposure to 30 ppm of nickel carbonyl for 30 minutes may be fatal. Initial symptoms are mild and transitory and include frontal headache and nausea, possibly accompanied by vomiting, dizziness, and occasionally sternal and epigastric pain. If exposure is severe, the initial symptoms are soon followed by other effects such as a cough, hyperpnea, cyanosis, pronounced weakness, and gastrointestinal symptoms. In extreme cases pneumonia, delirium, and death can occur (6).

Chronic Effects

Respiratory effects such as pulmonary irritation, asthmatic-like lung disease, pneumoconiosis, pulmonary edema, and pulmonary fibrosis have been reported in workers exposed to nickel dust and fumes. These exposures, though, were compounded by concurrent exposures to other compounds (1). Changes in olfactory function, rhinitis, erosions, perforations, and ulcers of the nose have been observed in workers employed in the electrolytic refining of nickel and in nickel refineries.

Epidemiological studies have conclusively demonstrated an excess risk of cancer of the nasal cavity and lungs in nickel refinery workers. The cancer hazard seems to be associated with the early years of nickel refining which involved heavy exposure to dust from relatively crude nickel ore. Suspicion of cancer has been focused primarily upon respirable particles of nickel subsulfide and nickel oxide, and upon nickel carbonyl vapor (3,5A).

A TLV of 0.1 mg/m^3 has been set for nickel metal and insoluble compounds of nickel. A TLV of 0.1 mg/m^3 and an STEL of 0.3 mg/m^3 has been set for soluble inorganic nickel compounds.

For nickel carbonyl, the TLV is 0.05 ppm and for nickel sulfide roasting, dust, and fumes, the TLV is 1 mg/m^3.

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RAC 33	SYSTEM											EFFECT							
NICKEL	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Nickel Ni	X	X	X			X		X				X					X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #34 - CADMIUM

Cadmium is a nutritionally non-essential but ubiquitous trace element that occurs naturally at low levels in the food chain. Smelters processing zinc, lead, and copper ores are the prime source of environmental cadmium contamination (11). Other significant and widespread sources include incineration of waste materials, burning of fossil fuels, use of phosphate fertilizers, and disposal of sewage sludge (7). Human exposure to cadmium occurs through inhalation, ingestion, or skin absorption, although the last appears to occur very rarely and only under very limited occupational circumstances. Inhalation is the more efficient route of absorption and is of primary interest from an occupational standpoint. However, except for cigarette smoking (cigarettes contain approximately 1.7 μg Cd/cigarette), ingestion is the major route to the total body burden in the general public (8). Although acute and chronic effects on humans are well documented from occupational studies, little is known about the chronic toxic effects of cadmium as normally encountered in food, air, and water. Also, in occupational studies, the actual dose received or length of exposure is not always reported.

The current drinking water standard in the USA is 0.01 mg/liter. The ACGIH (1) suggests a threshold limit value of 0.05 mg/m^3 for the oxide and salts and a ceiling value of 0.05 mg/m^3 for fumes. NIOSH (1976) has proposed a workplace time-weighted average limit of 0.04 mg/m^3 for both fumes and dusts, and a short-term limit of 0.2 mg/m^3 for not more than 15 minutes.

Acute Effects

Inhalation overexposure to cadmium fumes may produce symptoms, usually delayed for several hours, which include severe tracheo-bronchitis, pneumonitis, and pulmonary edema with a mortality rate of about 20%. Fatalities have occurred at concentrations of about 8 mg/m^3 for five hours. The lethal dose of cadmium oxide is about 2500 to 2900 mg min/m^3 (2-4) or 5 mg/m^3 (6) for an average 8-hr working exposure (8). Mild pneumonitis occurs between 0.5 mg/m^3 and 2.5 mg/m^3 for a 3-day period. The no-effect threshold for cadmium oxide fume is estimated to be <1 mg/m^3. The acute effects of other Cd compounds in man ($CdCl_2$, CdS, etc.) via inhalation have not been reported in the literature (8). Acute oral intoxication results in severe nausea, vomiting, diarrhea, muscular cramps, and salivation. This may be followed by shock and death within 24 hours. Acute renal failure and cardio-pulmonary depression followed by death may occur in 7 to 14 days. A rough scale of acute oral toxicity of Cd in man is presented in Table 2.

Table 2. Oral Toxicity of Cadmium in Man (8)

Dose (mg)	Effects
3-90	Emetic threshold
	Reported nonfatal incidents
15	Experimentally induced vomiting
10-326	Severe toxic symptoms but not fatal
350-3500	Estimated lethal doses
1530-8900	Reported lethal doses

Chronic Effects

The earliest and most distinctive indication of chronic effects of cadmium exposure is renal tubular dysfunction characterized by proteinuria (7,10). Other chronic effects include liver damage, emphysema, osteomalacia, neurological impairment, anemia, and testicular, pancreatic, and adrenal damage. The inhabitants of a region in Japan, after prolonged consumption of cadmium-contaminated water and rice crops, were struck by severe osteomalacia ("itai-itai" disease) characterized by lower back and leg pain (7). Recent evidence suggests that a strong nutritional deficiency may have played an important role however.

Chronic cadmium poisoning once established may progress without further exposure. Thus, workers exposed to 0.1 mg/m^3 or less may experience effects a decade later.

Although the analysis of cadmium in blood, urine, and hair can be routinely performed, Ellis et al. (5) indicate that these biological monitors of exposure are not reliable indicators of body burden for the individual worker, and direct _in vivo_ measurements of kidney and liver cadmium provide more accurate indices of cumulative exposure.

There is some evidence that high blood pressure is related to the body burden of cadmium. This relationship is still controversial, however (12).

A possible increase in prostatic malignancies in workers has also been reported. However, the small numbers involved, the influence of unmeasured factors such as smoking or marital status, and the frequency of the disease in the general population make the relation uncertain (9).

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RAC 34	SYSTEM											EFFECT							
CADMIUM	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Cadmium Cd	X	X	X	X	X	X	X		X	X	X	?		?	?		X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

Lead is a toxic metal with no known essential function in man. Its use as an antiknock additive in gasoline represents a major fraction of lead use in the United States, and motor vehicle emissions constitute the primary source of lead to the environment (1). Combustion of waste oil and solid wastes are major stationary sources of lead, along with iron and steel plants, smelters, battery manufacturing, and alkyl lead production. Although humans can be éxposed to lead via food, drink, or inhalation, uptake with food predominates under most conditions. About 200 to 300 μg of lead are taken up daily with food. Of that ingested, about 5 to 10% is absorbed by adults and somewhat more (up to 50%) by children, depending on diet. Besides natural levels, lead is introduced by processing, packaging, and raw food stock. Lead in paint makes it available by ingestion, especially to young children (1). Also, in regions of soft water, lead may leach from the plumbing.

Inhalation of airborne lead is of great concern and has led to measures limiting the lead content of gasoline. An average of 10 to 30 μg of lead is inhaled daily, although this value may be much higher in urban areas. Inhaled lead is much more efficiently absorbed - up to 50% - than is ingested lead (5). The highest and most prolonged exposures to lead are found among workers in the lead smelting, refining, and manufacturing industries (1). In work areas, the major routes of exposure are by inhalation and ingestion of lead bearing dusts and fumes.

Lead effects on humans have been well studied. Controlled environment laboratory studies on human volunteers have been performed (7). Also epidemiological observations of populations living in areas with differing air lead levels and occupationally exposed workers have been done. The ACGIH TLV for lead is 0.15 mg/m^3 and the STEL is 0.45 mg/m^3 (2). The National Ambient Air Quality Standard (NAAQS) for lead is 1.5 $\mu g/m^3$ over a 3-month period.

Acute Effects

Acute lead poisoning is very rare. Ingestion of large amounts of any soluble lead salt (especially acetate, carbonate, or chromate) results in irritation of the alimentary tract. If absorption is sufficient, then pain, leg cramps, muscle weakness, paresthesia, depression, coma, and death may follow within one or two days. The dose for fatal poisoning is usually greater than 30 g. Encephalopathy is a complication in about 50% of lead poisoning cases, and the mortality rate among these is 25%. Of those that recover, about one-third may have permanent neurological damage (9).

Chronic Effects

Characteristic symptoms of lead poisoning are produced in the hematopoietic system, central and peripheral nervous system, and kidneys. Although more than 90% of the lead body burden in man is contained in the bones, this lead is considered to be metabolically and probably also toxicologically inert (5). Blood lead levels are sensitive indicators of recent exposure. Normal blood levels are about 200 ppb; subclinical symptoms are noted in particularly sensitive persons at 400 to 600 ppb, and clinical symptoms can arise at more than 600 ppb (5). The subclinical effects of lead exposure are mainly neurological, including altered nerve conduction time, electromyographical abnormalities, behavioral disorders, and impairment of hand-eye coordination. Associations with mental retardation and hyperactivity have been reported, but not conclusively demonstrated (3).

Chronically exposed smelter workers have been shown to have a substantially excess number of deaths from chronic renal disease, cerebral hemorrhage, and hypertension (6). There is no convincing epidemiological evidence that lead causes cancer in man. However, induction of renal tumors has been demonstrated in laboratory animals (4).

Evidence indicates that among human populations the fetus and young children, particularly those under 3 years old, have an increased risk of experiencing adverse effects from lead exposure as a consequence of a higher rate of intestinal absorption and a high rate of brain growth and maturation (4). Roels et al. (8) showed sensitivities to lead to be of the order children > women > men. The U.S. National Academy of Sciences (4) mentions several sources of data on dose-response relationships for lead in men, but states that data are lacking for infants, preschoolers, and pregnant women.

The effects of organic lead compounds are slightly different from those of inorganic lead. Since organic lead compounds are lipid-soluble, they accumulate preferentially in the nervous system and can cause disturbances in sleep patterns, hallucinations, anorexia, vomiting, vertigo, muscular weakness, and tremor (5).

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RAC 35	SYSTEM											EFFECT							
LEAD	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Lead Pb	X			X	X	X	X		X			?	?		?		X		

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

RAC #37 - IONIZING RADIATION

Definitions

Radiation has been defined (3, p. 45) as the emission and propagation of energy through matter or space by means of electromagnetic disturbances (gamma radioactivity, xrays, light, microwaves, radiofrequency transmissions, etc.). The term has been extended to include streams of fast-moving particles (alpha and beta radioactivity, free neutrons, cosmic radiation, etc.). Nuclear radiation is that emitted from atomic nuclei in various nuclear reactions. Substances that spontaneously produce such emissions, chiefly alpha, beta, and gamma radiation, and neutrons, are called radioactive.

Alpha particles are the nuclei of normal helium atoms, consisting of two protons and two neutrons. Because of their inability to penetrate even a layer of air, alpha particles cannot be considered a hazard to human health unless emitted inside the human body as a result of ingestion or inhalation of radioactive materials. Beta particles are electrons (or positrons, their antimatter analog) and also have low penetrating power. Gamma rays are the highest-frequency form of electromagnetic waves. Neutrons are one of the constituents of atomic nuclei, the neutral (uncharged) analog of the proton. Gamma rays and neutrons exhibit varying degrees of penetrating power depending on their energies, and thus external sources of these are of concern for human health.

Ionizing and Non-Ionizing Radiations

Ionizing radiation displaces electrons from atoms or molecules, thereby producing ions (3, p. 28). Charged particles (e.g., alpha and beta particles) and electromagnetic radiation above a certain frequency (short-wave ultraviolet light, xrays, etc.) can directly ionize atoms. In addition, certain neutral particles (e.g., neutrons) can have significant indirect ionizing effects.

Non-ionizing radiation includes electromagnetic waves of lower frequency (longer wavelength) at all but the highest field strengths.

Examples include visible light, microwaves, radio frequency transmissions, and radiation from electrical distribution networks.

Only the human health effects of ionizing radiation are covered in this review.

Primary Biological Mechanisms

Ionizing radiation can directly disrupt cell nuclear material (DNA and RNA). More likely is the production (primarily from water) of free radicals. These in turn can disrupt, permanently or temporarily, the normal functioning of the cell.

Gamma rays and leptons (electrons and muons) generally interact with cellular material via ionization only. Other forms of radiation (e.g., neutrons, protons, and alpha particles) also can interact directly with the nucleus of atoms transmuting the nucleus and in the process emitting more ionizing radiation.

Units

The field of radiation protection has many special units. The most important and common ones are those measuring (radio)activity, absorbed dose, and biologically effective dose.

Activity. Activity refers to the number of nuclear disintegrations per unit time. It is proportional to the number of radioactive nuclei present divided by the half-life of that particular nuclide. The historic unit is the curie (Ci) equal to 3.7×10^{10} disintegrations per second. The SI (Systeme Internationale) unit is the becquerel (Bq) equal to 1 disintegration per second (1 Bq = 2.7×10^{-11} Ci).

Absorbed Dose. Absorbed dose is the energy deposited by ionizing radiation per unit mass of absorbing material (e.g., tissue). The rad is equal to 100 erg per gram. The SI unit gray (Gy) is 1 joule per kilogram (1 Gy = 100 rad).

Biological Dose Equivalent. The human health effects for a given absorbed dose depends on the type of radiation involved (alpha, gamma, etc.) and possibly the temporal distribution of that dose (e.g., whether single exposure or protracted over lifetime). Multiplication of absorbed dose by factors measuring relative biological effectiveness of a radiation type (Q) and measuring relative temporal effectiveness as well as other modifying considerations such as spatial distribution within the tissue (N) yields a dose which is independent of radiation type and temporal distributions (all other relevant factors being equal).

The historic unit is the rem (radiation equivalent man) and the SI unit is the sievert (Sv) (1 Sv = 100 rem). Since the multiplicative factors are dimensionless, the gray and sievert (or rad and rem) possess the same fundamental units but measure distinctly different quantities.

Effective Dose Equivalent. Finally, the dose equivalent received by each organ (tissue) can be weighted by a factor (w) which measures relative sensitivity of the tissue to radiation-induced cancer. If the results are summed over all tissues, the result is termed the effective dose equivalent to the whole body. The units are the same as dose equivalent, so care must be taken to understand which quantity is being measured.

Association of Types of Effects With Dose Level

Acute, nonstochastic human health effects are associated with high dose levels of ionizing radiation. On the other hand only chronic, stochastic effects are associated with low levels. It is understood that if an individual survives a high radiation dose, stochastic effects may subsequently develop.

Following a discussion of sources, the remainder of this article is divided into two sections, one on high-dose effects and the other on possible low-dose effects. Specialized terms are defined, dose level ranges indicated, possible human health effects enumerated, dose-response functions, if any, given, and applicable federal protection standards listed.

Sources and Natural Background

Humans are, and always have been, exposed to radiation of a natural (not man made or induced) origin. The sources of natural irradiation can be grouped into three general categories, each of which can be further subdivided (1).

Primary cosmic rays are extraterrestrial elementary particles (e.g., protons). These cannot penetrate the earth's atmosphere to sea level, but primary cosmic rays can also interact with the atmosphere producing, directly or indirectly, penetrating secondary cosmic rays (e.g., mu-mesons). Cosmic rays irradiate the whole body.

Interactions of cosmic rays can also produce so-called cosmogenic radionuclides. After being produced, these nuclides distribute in the biosphere and eventually contribute to the internal irradiation of humans. The most important cosmogenic radionuclides are carbon-14, beryllium-7, sodium-22, and hydrogen-3 (tritium).

The final group is the primordial radionuclides. These long-lived nuclides have been present since the formation of the earth. They in turn can be divided into two parts: (a) light radionuclides (e.g., potassium-40 and rubidium-87), and (b) the naturally occurring decay chains, those headed by uranium-238, uranium-235, and thorium-232. Gamma-ray decays of any of these radionuclides externally irradiate the body; any decay mode internally irradiates.

The following table summarizes the typical amount of effective dose equivalent from each of the groups. There are very large variations from location to location.

Natural Background

Estimated per Caput Annual Effective Dose Equivalent From Natural Sources in Areas of Normal Background (2)

Source		Effective dose equivalent mSv a^{-1}	rem/year
Cosmic rays		0.301	0.0301
Cosmogenic radionuclides		0.015	0.0015
Primordial radionuclides			
^{40}K, ^{87}Rb		0.306	0.0306
^{238}U, ^{235}U series		1.044	0.1044
^{232}Th series		0.326	0.0326
	Total	2.0	0.200

By far the largest man-made source of human irradiation is medical diagnosis and therapy. On a per caput basis, medical exposures amount to about 20% of the magnitude of natural exposure. In contrast, the other sources listed below are of the order of 1% of natural exposure.

Coal contains trace amounts of the uranium and thorium series radionuclides, and potassium-40 at levels comparable to normal soil. When pulverized or burned, the contained radon (a radioactive noble gas) is released to the atmosphere. The ash content of coal is about 10%. Therefore, the radionuclide concentration in bottom ash will be ten times the level in the original coal. Concentration of certain radionuclides may be even higher in fly ash because of enhancement mechanisms. Humans may be exposed to minute levels of radiation if exposed to materials made from coal ash or from fly ash emitted to the atmosphere.

Other non-nuclear energy sources with related radioactivity are geothermal energy and natural gas. In the case of geothermal power plants, some radon is emitted to the atmosphere causing slightly elevated exposures to the local population. The burning of natural gas can elevate radon levels in unventilated kitchens.

Another cause of enhanced exposure to radon similar to the situation with cooking with natural gas is the fact that some present day populations of humans live in relatively tight houses. This allows radon and its radioactive daughters which emanate from underneath the house or from building materials to build up to levels well above ambient outdoor levels. Gamma-ray-emitting nuclides in building materials, especially those of the uranium and thorium series, irradiate humans directly.

Phosphate rock generally contains concentrations of the uranium-238 series nuclides about twenty times that of normal soil. Enhanced human exposure is associated with the processing of phosphate ore, especially the production of elemental phosphorus, the use of fertilizer, and the use of by-product gypsum.

Cosmic-ray flux increases with altitude. Therefore, aircraft passengers and airline employees experience higher exposure to cosmic rays during flights, as do people living at high altitudes.

Finally, there may be exposure associated with miscellaneous products or devices: x-rays from television sets or scanning devices, radioluminous devices, heart pacemakers, smoke detectors, etc. Some of these sources involve man-made radionuclides, for example, americium-241 used in many smoke detectors.

Nuclear energy technologies produce radioactive substances found in nature only at infinitesimally small levels. Nuclear fission yields fission products (e.g., strontium-90, iodine-131), transuranic radionuclides (neptunium, plutonium, etc.), and neutron-induced radionuclides (e.g., manganese-54, nickel-63). Nuclear fusion produces (or uses as fuel) very light radionuclides and also induces radionuclides by neutron activation. The supply side of the nuclear fuel cycles release small amounts of the naturally occurring uranium and thorium-232 decay series. Reactor operation, fuel reprocessing, and decommissioning involve very small releases of fission products, transuranics, and induced radionuclides. Only in nuclear war, an unusual occurrence connected with an atmospheric test of a nuclear device, or a very severe accident at a nuclear power plant from which the immediate population is not evacuated, can exposure of any member of the general population be significant, that is larger than one year's equivalent of natural background.

Certain occupational categories can be exposed to annual extra doses of radiation comparable to natural background. These jobs are related to the production of or products of nuclear fission, scientific research, x-ray machines, or high altitude flight.

Standards

National regulatory bodies have adopted comparable standards for radiation protection. An effective dose equivalent of 50 mSv (5 rem) per year is the occupational dose limit. Exposure of any individual of the general public should not exceed 50 Sv a^{-1} (5_mrem/yr) from the routine emissions of regulated sources. Actual exposures are generally an order of magnitude lower than the regulations. Guidelines state that in no instance shall a dose to an individual exceed 5 mSv (500 mrem). There are exceptions to and variations on the general guidelines which involve the particular type of radiation, the target or critical organ, the specific radionuclides involved, the age and sex of the individual, and even the source of the radiation. For example, nuclear power plants are regulated, but radioactive emissions from coal burning plants and medical exposures are not.

Acute Effects

Acute effects of irradiation are nonstochastic in nature. There is usually a threshold below which no clinical effects would be observed in any human being. As the dose level is increased, all human beings would exhibit about the same degree of effect at a given dose and the severity of the dose would increase with increasing dose.

In addition to dependence on total dose, the severity of the effect usually depends on the rate at which the dose was applied and the fraction of the organ in question irradiated. Severity increases with dose rate and fraction irradiated.

Finally, certain nonlethal acute effects may continue at some level to normal end of life (e.g., loss of hair). And, if the person does survive the acute effects, he will be at risk from the stochastic health effects described later.

This summary of acute effects of radiation below is taken from the Reactor Safety Study (4).

When exposed to a very large dose of whole-body irradiation, death is most likely to occur from damage to the red bone marrow (acute anemia) in combination with damage to the lymphoid tissue (reduced defense to infection) and damage to the vascular system (increased bleeding hazard). There is general agreement that in the absence of special treatment the 60-day LD_{50} is in the range 300 to 400 rad. The LD_{10} to LD_{90} range is about 200 to 500 rad. No deaths are expected below about 150 rad. The exception is prenatal death. One day after conception the median lethal dose is about 85 rad, with a minimal lethal dose as low as 10 rad. The sensitivity of the embryo/fetus decreases to adult values by the end of term.

With extensive medical treatment the 60-day LD_{50} can be increased to almost 1000 rad. Treatment includes transfusions, bone marrow transplants, antibiotics, and protection from infection.

Chronic Effects

The two chronic effects of most concern in relation to radiation are cancer and, so-called, genetic effects, that is, adverse health consequences in the offspring of the irradiated person. At this time it is impossible to determine either experimentally or epidemiologically what the probability of the effects are at very low dose levels (1 rem and below). In the absence of definitive data, observed effects in humans (or animals) from high doses of irradiation are extrapolated downwards. Especially significant in this regard have been the Japanese survivors of the atom bomb, groups with large medical exposures, and certain special occupational groups, e.g., radium dial painters and uranium miners. Since excess effects to an extra dose (of say 10 mrem) are unknown, much controversy exists on whether the extrapolation predictions are ten times too low, or ten times too high, or more.

Different tissues have shown different sensitivities to radiation-induced cancer. Especially prominent at high doses have been female breast cancer, leukemia due to whole-body irradiation or bone seeking radionuclides, and lung cancer due to inhalation of radioactive materials.

The BEIR III Committee (NAS 80) dose-response function at low doses for cancer mortality, based on the Japanese survivors, is 67 x 10^{-4} per sievert effective dose equivalent using a linear-quadratic fit to the data and an absolute risk projection. Using a linear fit and a relative risk projection, the dose-response coefficient is 430 x 10^{-4} per sievert. An even lower value would be obtained with a pure quadratic fit. The shape of the dose-response curve is certainly not universal over all radiation types (e.g., gamma vs alpha emissions) or all tissues. The dose-response for nonfatal cancers is comparable but even more uncertain.

Genetic disorders in humans due to low levels of extra radiation is an even harder field of study. Extrapolating primarily from high-dose animal data BEIR III estimated a first generation increase of 5 to 75 x 10^{-4} serious genetic disorders in liveborn offspring per sievert of parental exposure. At genetic equilibrium, the figure is 6 to 110 x 10^{-3} per sievert received in each generation.

Disruption of the normal proliferaton of the intestinal epithelium may be fatal. Mortality from this cause commences at doses above 1000 rad whole body or 1500 rad to the abdomen.

Nonlethal health effects include the prodromal symptoms, a generic term for anorexia, nausea, vomiting, and diarrhea associated with radiation exposure. About half the exposed people will show prodromal symptoms at an instantaneous dose of 200 rad.

Other nonlethal effects are radiation dermatitis, loss of hair, cataracts, impairment of the immune system, male fertility impairment, and congenital malformation and growth retardation in the prenatally exposed. There are no established effects observed below 100 rad except that decreased sperm count has been observed at levels as low as 10 rads.

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RAC 37	SYSTEM											EFFECT							
IONIZING RADIATION	Cardiovascular	Pulmonary	Skin	Muscular-Skeletal	Hematological	Gastrointestinal	Renal	Eye/Ear/Nose/Throat	Central Nervous System	Endocrine	Hepatic	Cancer	Teratogenic	Mutagenic	Reproductive	Allergen	Irritant	Anesthetic/Narcotic	Asphyxiant
Ionizing Radiation	X	X	X		X	X		X		X		X	X	X	X				

X = known human effect
? = based on animal data, experience with similar compounds, or inconclusive human data

APPENDIX A
RISK-ASSESSMENT CATEGORIES

An adequate chemical-by-chemical health effects risk assessment is precluded because of the vast number of chemicals involved; the inability to characterize these compounds fully; the fact that many are chemically transformed in the environment; and gaps in toxicological information. Accordingly, the theme developed in this EPA program is to group pollutants in broad, chemically defined risk-assessment categories (RACs). Table A-1 lists criteria developed by EPA and Oak Ridge National Laboratory for determining these categories.

Table A-1. Criteria for Determining Risk-Assessment Categories

a. Engineering Relevance. A goal of risk assessment is to provide useful guidance to industry. Therefore, process streams must be characterized in terms of their RAC content so that plant designers and operators can apply the results of the risk assessment.

b. Analysis Capability. The categories must correspond to practical chemical characterizations of the products and effluents of interest as revealed by biotesting. RACs that are divided more finely than existing chemical and biological analysis schemes will not be useful.

c. Completeness. All constituents of the industry's products and effluents must be included in the system of RACs.

d. Nonoverlap. The RACs should be mutually exclusive; i.e., none of the constituents should be assessed twice. Chemicals with multiple functional groups can be handled by assigning them to the RAC which they follow during chemical fractionation.

e. Data Compatibility. The correspondence between the RACs and commonly used chemical classes should be clear enough to allow use of existing data and regulatory standards in the risk assessment.

The current listing of 38 RACs is shown in Table A-2. In practice it is difficult to devise groupings that fully satisfy all the above criteria. Risk-assessment applications are evolving; those described here are presented in an example situation: development of synthetic fuel technologies. This application may lead to modifications of the methods or the manner in which they are used, including possible restructuring of RACs; e.g., dividing some RACs into subgroups.

The RAC approach initially does not consider synergistic or other interactive effects. While interactions are known in some cases to be important, no available method takes all potential interactions into account in a broad approach such as this. This is an important area for further investigation and is addressed in more detail elsewhere in this program.

Table A-2. Risk-Assessment Categories

RAC Number	Category	Description
1	Carbon monoxide	CO
2	Sulfur oxides	SO_x
3	Nitrogen oxides	NO_x
4	Acid gases	H_2S, HCN
5	Alkaline gases	NH_3
6	Hydrocarbon gases	C_1–C_4 alkanes, alkenes, alkynes, and cyclo compounds; bp <#20°C
7	Formaldehyde	HCHO
8	Volatile organochlorines	To bp #120°C; CH_2Cl_2, $CHCl_3$, CCl_4
9	Volatile carboxylic acids	To bp #120°C; formic and acetic acids only
10	Volatile O and S heterocyclics	To bp #120°C; furan, THF, thiophene
11	Volatile N heterocyclics	To bp #150°C; pyridine, piperidine, pyrrolidine, alkyl pyridines
12	Benzene	Benzene
13	Aliphatic/alicyclic hydrocarbons	C_5(bp #40°C) and greater; paraffins, olefins, cyclo compounds, terpenoids, waxes, hydroaromatics
14	Mono/diaromatic hydrocarbons (excluding benzene)	Toluene, xylenes, naphthalenes, biphenyls, alkyl derivatives
15	Polycyclic aromatic hydrocarbons	Three rings and greater; anthracene, BaA, BaP, alkyl derivatives

Table A-2. Risk-Assessment Categories (cont.)		
RAC Number	Category	Description
16	Aliphatic amines	Primary, secondary, and tertiary nonheterocyclic nitrogen, $MeNH_2$, DiMeNH, TriMeN
17	Aromatic amines (excluding N-heterocyclics)	Anilines, naphthylamines, aminopyrenes; nonheterocyclic nitrogen
18	Alkaline nitrogen heterocyclics ["azaarenes"] (excluding "volatiles")	Quinolines, acridines, benzacridines excluding pyridines
19	Neutral N,O,S heterocyclics (excluding "volatiles")	Indoles, carbazoles, benzofurans, dibenzothiophenes
20	Carboxylic acids (excluding "volatiles")	Butyric, benzoic, phthalic, stearic acids
21	Phenols	Phenol, cresols, catechol, resorcinol
22	Aldehydes and ketones ["carbonyls"] (excluding formaldehyde)	Acetaldehyde, acrolein, acetone, benzaldehyde
23	Nonheterocyclic organo sulfur	Mercaptans, sulfides, disulfides, thiophenols, CS_2
24	Alcohols	Methanol, ethanol
25	Nitroaromatics	Nitrobenzenes, nitropyrenes
26	Esters	Acetates, phthalates, formates
27	Amides	Acetamide, formamide, benzamides
28	Nitriles	Acrylonitrile, acetonitrile
29	Tars	
30	Respirable particles	
31	Arsenic	As, all forms
32	Mercury	Hg, all forms
33	Nickel	Ni, all forms
34	Cadmium	Cd, all forms
35	Lead	Pb, all forms
36	Other trace elements	
37	Radioactive materials	^{226}Ra
38	Other remaining materials	

PREFACE

This project was begun in the Medical Department of Brookhaven National Laboratory under the direction of M.E. Miller, then Principal Investigator of the EPA Synfuels Health Effects Clinical Program. A substantial amount of preliminary work was done at that time by C. Kramer, including a series of computerized bibliographic searches, gathering of literature, and preparation of summary tables of the kinds of effects expected from each Risk-Assesssment Category (RAC). The work drew heavily on a parallel review of animal literature being conducted in the Biomedical and Environmental Assessment Division (BEAD) and on the earlier experience of BEAD in working with the RAC concept and organizing chemicals within that structure.

In June 1983, responsibility for the project was transferred to BEAD as part of the EPA Health Risk Analysis Program (L.D. Hamilton, Principal Investigator). In the meanwhile, Mrs. Kramer had also transferred to the BEAD staff, and was given responsibility for the project.

Despite the preliminary work that had been done, it was difficult to do justice to the task and complete a report in the allotted time (September 1983). It was agreed upon with A.A. Moghissi, the EPA Project Officer, that, where authoritative reviews already existed, they would be summarized in 3 to 5 pages and the literature search would cover only information published after the review. The review of each RAC would vary -- from one page, where very little human information exists, to as many as twenty pages, where important studies exist that have not been previously reviewed. The expectation was a 100- to 200-page document.