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A FOLLOW-UP STUDY PROGRAM FOR PERSONS IRRADIATED
IN RADIATION ACCIDENTS

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ABSTRACT

Clinical and epidemiologic follow-up studies of survivors of radiation accidents are a major part of the program of the Radiation Emergency Assistance Center and Training Site (REAC/TS) in Oak Ridge, Tennessee, where training is provided for physicians and paramedical staff concerned with radiation-accident victims. Guidelines have been developed for clinicians and epidemiologists to do follow-up studies after accidental exposures. The human radiobiological data so obtained are used to improve clinical care and emergency planning in nuclear-energy production. Other aims of these studies are to provide the best prophylactic and anticipatory care for possible late radiation effects, and to continually upgrade radiobiologic risk estimates by epidemiologic investigations.

Routine annual clinical follow-up studies are recommended for those survivors who were severely injured, and others who showed clinical or laboratory evidence of the acute radiation syndrome. The extent and protocol for medical examinations will be described. In industrial plants located in the United States where annual physical examinations are routine, medical results obtained about the status of such persons are reported to REAC/TS. Persons involved but not seriously exposed in radiation accidents are contacted annually by phone or letter to ascertain their whereabouts and health status for epidemiologic data collection. Dosimetric guidelines categorizing the follow-up groups will be defined. These are related to total-body exposure levels, extent of local exposures, and residual body and lung burdens of transuranic elements. The follow-up studies are continued for life. The records are deposited in a centralized national radiation-accident registry in REAC/TS where the information is available to clinicians, radiobiologists, and epidemiologists.

INTRODUCTION

One of the major programs of the Radiation Emergency Assistance Center and Training Site (REAC/TS) in Oak Ridge is a life-time morbidity study of survivors of radiation accidents. The central component of this program is the United States Radiation Accident Registry. REAC/TS has been designated to manage that registry and to establish a national repository for the United States Energy Research and Development Administration (ERDA). Because REAC/TS is also involved in the direct medical management and health physics support of persons exposed or suspected of having been exposed in radiation accidents, its staff also maintains a second registry of its own cases and their histories. A third registry, which is largely an anecdotal library, contains what information is available worldwide in the open literature and in official documents on radiation accidents and their medical consequences. These three registries provide the factual basis for the training courses in Radiation Accident Management which are given by the REAC/TS staff with the help of their consultants¹ several times each year for physicians, health physicists, and emergency medical teams [1]. These data also are used to identify needs for better knowledge and improved methods for the treatment of various kinds of radiation injuries.

¹In addition to the Medical and Health Sciences and the Special Training Division staff the extramural seminar staff lecturers have been W. R. Albers, Chief Occupational Health Physician, Division of Operational Safety, ERDA, Washington; W. R. Bibb, Chief of the Research and Development Branch of the Research and Technical Support Division, ERDA, Oak Ridge Operations (ORO); Victor Bond, Associate Director, Brookhaven National Laboratory; W.W. Burr, Deputy Director, BER, ERDA, Washington; James Hogan, Head, Internal Medicine and Hematology, St. Barnabas Hospital, Livingston, New Jersey; T. A. Lincoln, Director, Health Division, ORNL, Oak Ridge; George A. Poda, Medical Superintendent, E. I. duPont de Nemours & Co., Savannah River Plant, Aiken, South Carolina; E. L. Saenger, Director, Radioisotope Laboratory, Cincinnati General Hospital; J. B. Storer, Director, Biology Division, ORNL; George L. Voelz, Director, Division of Health Research, University of California, Los Alamos Scientific Laboratory, New Mexico; and Niel Wald, Chairman, Department of Industrial Environmental Health Sciences, University of Pittsburgh.

All accident registries depend upon an active follow-up program for continuing growth. New information is sought constantly to improve the accuracy of the records and to make them as complete as possible. This paper describes our follow-up program, how it operates, and the role it plays in a national effort to minimize radiation accidents and their aftereffects.

REGISTRY PROGRAM

General Aspects

Medical and epidemiologic follow-up studies of accidentally irradiated persons provide accurate human radiobiological information for scientific use and public dissemination. Well planned studies of immediate, subacute, and late effects of radiation continue to be needed to assess the magnitude of radiation-related health problems of the nuclear age.

Radiobiological facts derived from these studies help us to deal with the hazards of radiation by refining the clinical care of accident victims and by improving our planning for emergencies arising in the production of nuclear energy, in medical institutions, and in research laboratories. Other aims of these studies are to provide the best prophylactic and anticipatory care for possible late radiation effects and to continuously upgrade radiobiological risk estimates by epidemiologic investigations. All information obtained is incorporated into the data bank and continuously evaluated.

Fortunately, the number of persons injured by radiation in accidents is small. However, the very rarity of such individuals makes any information about them extremely valuable; data on the clinical course of each one are needed to provide a totality of experience to guide physicians treating irradiated persons. The information in the Registry is also used by radiation biologists and radiation safety experts to continually reevaluate the radiosensitivity of man and the adequacy of protection standards and safety measures.

Selection Criteria for Registrants

Today management of data files that contain medical information is complicated. In the past, little effort needed to be extended in maintaining the anonymity of radiation accident victims, and information about them could be disseminated in the scientific and public press. Recently, firmly established

legal constraints in the United States and other countries have produced guidelines for registries, such as these described here, to protect the identity and privacy of registrants. Medical information about them can be used in scientific reports only with their written permission. The Freedom of Information Act, although in part intended to prevent governmental and corporate management from shielding from the lay press and others information potentially useful in making a case against governmental programs and corporate management practices, does not allow the disclosure on demand of medical records in data banks such as ours. However, we can make the Registry meet the needs for medical information by abstracting its records and collecting the facts to answer specific questions addressed to it by responsible persons or organizations.

Living registrants in the Registries who may, for example, decide at some remote date that they do not want to be a statistic can stop their participation in the registry and its follow-up program at any time. Legally, however, information about a dead person which does not affect living members of his family is open to public scrutiny and scientific medical usage. Data acquisition about living radiation accident victims depends on recruitment of the individual concerned and obtaining his "informed consent" to participate in the Registry program.

Because of limitations of funds for the operation of such registries, not all persons exposed in radiation accidents are recruited into the follow-up program of medical and epidemiologic surveillance. Persons to be recruited for follow-up must have received doses decidedly above permissible occupational levels, with some certainty that acute or subacute early clinical or laboratory effects will be observable. All others are simply registered and their estimated exposures are recorded as published in the annual overexposure registry report of the Bureau of Radiological Health of the Department of Health, Education, and Welfare.

For the purposes of recruiting individuals into the Radiation Accident Registry, "significant" accidental ionizing radiation exposures are defined as levels at which early biological changes and clinical symptoms might be expected. Details of a specific radiation accident are registered as soon as we learn of the event; and, for each accident, every person who received any radiation exposure is listed in the Registry.

It is intended to obtain medical follow-up information annually on persons exposed to doses of ≥ 25 rads, total body irradiation, and on certain other groups as shown in Table I.

FOLLOW-UP PROGRAMS

Levels of Follow-up

Our follow-up program is carried out on three different levels (Figure 1). The REAC/TS staff obtains medical information directly from radiation exposed persons treated at the REAC/TS facilities or on a consultant basis. In most instances their extended follow-up is continued by the Oak Ridge staff. The second level of data collection for the Registry Program encompasses persons followed by Nuclear Regulatory Commission (NRC) physicians, industrial or private physicians, and by Energy Research and Development Administration plant physicians. Data from these sources are reported to the Registry with the consent of the registrant. The third mode of following the medical history is through direct communication between REAC/TS staff members and the exposed person. And finally, anecdotal information on radiation accidents that occur in foreign countries is followed by the Registry through scientific publications and the news media.

Type of Information Required

The information in the Registry for each recruited person includes the following: estimates of dose, by type of radiation for each part of the body exposed, and details of the dose calculations; a complete medical history before and after the accident; copies of all relevant hospital, laboratory, and physicians' records covering the period of observation for signs and symptoms directly related to the accident, and their management; and copies of records of all subsequent physical examinations and hospitalizations, including pathology reports and slides of tissue specimens as they appear to relate to the radiation injury.

The exposure information generally becomes available from the accident investigation reports required by state or federal governments. However, the rest of the information can be obtained only with the written consent of the patient.

Recruitment and Relationship with the Registrant

Recruitment of persons into the follow-up program is national in scope, and it is under the direction of the Division of Biomedical and Environmental Research, ERDA, and by official agreement has the cooperation of the Regulatory Division of the Nuclear Regulatory Commission (NRC). There is a close working relationship with NRC, and individual states. All accidents occurring in the private industrial use of radioactivity are reported to us; after the exposed persons have been treated, an investigation of all aspects of the accident is conducted under the guidelines of ERDA (Division of Safety, Standards, and Compliance), NRC, or the agreement state. On completion of the investigation and official medical surveillance or therapy, the investigative consultant physician (ERDA, NRC, or agreement state) explains the nature of the follow-up program to the potential registrant. After he has signed the "informed consent" form and identified his private physician to us, the REAC/TS staff gets in touch with him and makes a schedule for future follow-up contacts. The frequency of these are determined by the nature of any residual injuries, and the severity of the initial radiation-induced damage.

There are two major categories of registrants: one consists of those whose irradiation levels exceed lower limits of exposure set arbitrarily to exclude those persons with little or no probability of developing acute or subacute effects and for whom all of the information is obtained from outside sources. The second category encompasses persons referred directly to us for medical management or consultation. A third group, entered into a supplementary registry, are people involved in radiation accidents outside the United States. We are also maintaining still another data bank on persons exposed to acceptable occupational radiation levels; this latter group is of little concern in this paper. Figure 1 shows the sources of patients, types of registries, follow-up, and research programs of REAC/TS.

We are informed of accidents as they occur in laboratories supported by the Energy Research and Development Administration; we receive information from the Nuclear Regulatory Commission; and we are contacted by agencies that are responsible for radiation accidents in the individual states. Based on the release form, copies of employment records and medical records are obtained. It is much easier to recruit a person into a follow-up program during the early phase of follow-up since a

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beneficial relationship of trust and confidence between the accident survivor and the physician should have developed at that time. It is especially important to start a follow-up program early in persons who have received a relatively mild overexposure rather than to call them back into the program years later after they had initially been informed that the exposure was probably of no significant consequence to their lives and health.

At the time of the first contact by the Registry an approximate date for these annual contacts is established for the convenience of the Registrant. At the time of the annual contact the registrant is asked about his health during the past year. If he has had any illnesses, or physical examinations, he is requested to have the medical records made available through his physicians. Any expense involved in obtaining these records is borne by the Registry.

There is the risk of losing patients from follow-up especially in the United States where people move their residence much more freely than elsewhere; but an early commitment to participation in the program should make a fairly complete follow-up possible. Persons involved but not seriously exposed in radiation accidents, i.e., less than 25 rads total body exposure or less than one-half maximum permissible body or organ burden, will be contacted annually by phone or letter to ascertain their whereabouts and health status for epidemiologic data collection.

Recommended Follow-up Studies

Annual physical and laboratory examinations are desirable. These may be performed at industrial plants where annual physical examinations are routine, by private physicians, and in a few cases by REAC/TS personnel. Persons who, because of retirement, have discontinued routine annual industrial medical examinations will be asked to continue the follow-up through their previous employer or private physicians.

With each annual check-up the medical history is updated with emphasis on skin changes, and early symptoms of cancer. The history should also include questions concerning the health status of any children of the registrant born after the radiation accident. Attention should be given to job performance, recreational physical activities, mental and psychological status, and the marital-sexual sphere.

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The physical examination focuses on early detection of cancer. In cases with a history of incorporation of transuranium elements which have specific tissue concentration sites, examination of these target organs is emphasized, and perhaps more aggressive surveillance with specific diagnostic procedures may be indicated, i.e., sinus cancers after radium incorporation.

A blood leukocyte count and differential are done routinely. Special attention is given to absolute granulocyte and lymphocyte counts, basophilia, and the emergence of immature cells. We do not feel that routine examination of bone marrow is necessary. Abnormal leukocyte morphology is an indicator for it, of course.

Cytogenetic analysis of lymphocyte chromosomes is a most useful tool in determining the radiation dose of accident victims, even if the exposure antedates the chromosome analysis by years. However, at this time no characteristic chromosome abnormalities have been found to be of predictive value for leukemia or cancer. There are a number of malignant diseases; for instance, chronic granulocytic leukemia, Burkitt's lymphoma, and some cases of acute leukemia, in which the malignant cells display chromosome abnormalities. Although minor clones of cytogenetically aberrant cells have been seen in lymphocytes and marrow cells from some persons with previous radiation exposure, in no instance have these abnormalities been shown to predispose the affected cells to neoplastic transformation. We anticipate that annual cytogenetic examination may, with increased awareness and new techniques, such as chromosomal banding, develop into a useful part of the follow-up protocol.

While interesting biochemical serum abnormalities are found in a variety of patients with different types of advanced cancer, it is questionable at present whether any test or battery of tests can be useful for detection of early cancer in asymptomatic patients. Biochemical tests are generally not part of the examinations unless the medical history or clinical findings should indicate the need for them.

A free dialogue between the patient and the physicians should be started in the early post-accident period. All the potential sequelae of radiation damage should be discussed frankly and competent answers given to questions.

One problem in this continued discussion may be that of divided responsibility between the physician dealing with the

radiation accident and the patient's private physician. Good communication is the solution. We hope that the training provided by institutions such as REAC/TS will give industrial physicians an objective perspective of radiation effects on man and a confident basis to deal with the problems that arise.

Costs for Follow-up Program

The costs may be considered under three different categories. First, the procedures that are part of any good health maintenance program; depending upon whether or not such a program already exists regardless of radiation accidents, this may or may not cause a significant increase in cost. Second, procedures that are being done for research purposes, such as serial cytogenetic or special biochemical tests. The costs here would depend on the nature of the research project and would need to be paid out of research funds. Third, there are the costs associated with establishing the Registry and collecting and analyzing the data. Depending on travel costs and on whether examinations that are otherwise not done must be paid for, the costs may vary widely. A modest follow-up program could be done by mail with a relatively low budget; even simple survival statistics would be valuable for the Registry. Who should pay for the program; the government, private industrial companies, or insurance companies? This may vary from country to country. The most practical solution is probably a continued follow-up by the employer of the irradiated person during the entire employment and extending into the retirement of the employee.

RESEARCH PROGRAMS

Epidemiological Studies

While the early effects of high level radiation constitute rather characteristic syndromes, the late effects consist only in a change in incidence of naturally occurring diseases. Thus, the late effects can never be tied to radiation in the individual case, and a population study with a suitable control group appears necessary. Ideally members of a control group for radiation accident victims would be of the same sex and age, have the same type of occupation, live in the same general environment, and have similar life styles and habits. These requirements are difficult to meet, and compromises will have to be made.

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Instead of trying to assess cause and effect in irradiated persons by means of suitable unirradiated control groups, we have elected to design our follow-up program as a dose-response study in which "dose groups" will be categorized according to dose, total or partial body irradiation, continued or acute exposure, and type of radiation. Thus, the individual dose groups, 25-49 rad, 50-99 rad, 100 to 149 rad, etc., and 1/2 to 1, >1 to 2, >2 to 3 Maximum Permissible Burden (MPB), etc., can be compared with each other, decreasing the emphasis on or even eliminating the need for "normal" control groups. The study will focus more on morbidity than mortality; and the Registry, based on valid medical observations, may lead to the detection of new radiation effects and provide a better understanding of RBE. Good determinations of air dose, skin dose, and absorbed dose are of cardinal importance.

We believe that this approach is more likely to yield useful scientific and practical medical information at considerably lower costs than other attempts that would include control groups based on disputable selection criteria. In any event the success of a long-term follow-up study would be limited because of the small number of persons involved, and it will not be possible to prove or disprove a small change in the incidence of late neoplasms or genetic effects. But if a large increment can be ruled out, this will be of considerable reassurance to accident survivors.

Cytogenetic Studies

Peripheral blood lymphocyte karyotypes are examined in persons followed by the REAC/TS staff and on a consultant basis primarily for dosimetry purposes. The dose estimates, based on chromosome analyses are compared with the dosimetry information derived from film badges and other devices. Special attention is given to dose distribution: total body exposure versus partial body radiation, and external radiation versus exposure from incorporated radionuclides.

If direct bone marrow preparations can be included in the cytogenetic analysis, attention is also focused on the detection of clones of cells with chromosomal abnormalities. No specific clues or methods are now known to be of value in detecting preneoplastic chromosomal derangements that could be predictive in following radiation accident survivors with the intention of early detection of leukemia or cancer.

Special Problems

The REAC/TS research program includes a special project on application of Diethylenetriamine-pentaacetic acid (DTPA) as a chelating agent in decorporation measures. REAC/TS has the United States supply of Ca-DTPA and is responsible for the distribution and safe application of this agent. Our main concern is quality control and biomedical detection of early and late effects in persons to whom it has been given; these are a special group in our follow-up program.

The problem of radiation damage to the extremities, often resulting in gangrene and loss of limbs, is another subject of our research. We are testing radioisotopic methods in animals to detect the final line of demarcation of necrosis. Definitive amputation at a relatively early time after radiation insult should preserve more and better function of a limb and yield better cosmetic results than the multiple amputations guided by progressing gangrene, which prolong morbidity.

DISCUSSION

With continued acquisition of data through our Registry we should be able to supplement the vast reservoir of radiobiological data in animals with valid observations in humans, so that adequate plans can be made for safety, and for skillful management of those radiation accidents that can not be completely avoided.

Each human population group has certain disadvantages from a scientific-epidemiologic point of view, such as pre-existing disease, unknown dosimetry, and unrelated health problems. The greatest limitation is the lack of adequate numbers for statistical evaluation in each exposure group. For this we should be thankful. Nevertheless, the approach described in this paper offers a possibility for demonstrating even an extremely low incidence of dire late effects, should such occur, even though it is not likely to document a small increment of radiation-induced neoplasms. Thus, while not solving problems of threshold, the study should produce data reassuring to the patients involved and the public. Indeed, the data so far available tend to provide such reassurance.

It is distressing to scientists that the general population seems unaware that radiation injury has been better studied than almost any other environmental hazard. The tendency for anti-nuclear propaganda to demand a specific exposure level

below which there would be zero amount of damage is unreasonable in view of the fact that no such levels are known for lead, sulfur dioxide, or other pollutants. While it has seemed fruitless to try to convince the public that those who advocate the use of nuclear energy are not in a conspiracy to destroy the world, it has been possible to help radiation workers to develop a rational attitude about the hazards of their occupational environment.

We hope to be able to report on the progress and some results of this follow-up program at a later time and then consider whether this approach can be developed to an acceptable model for other institutions, a model which could form the basis for a larger international follow-up program with central data collection perhaps sponsored by the International Atomic Energy Agency, the World Health Organization, or the United Nations.

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REFERENCES

- [1] LUSHBAUGH, C.C., et al., "'REACTS:' A Pragmatic Approach for Providing Medical Care and Physician Education for Radiation Emergencies Requiring Decontamination." (Proceedings of IAEA Symposium on Diagnosis and Treatment of Incorporated Radionuclides, Vienna, 1975), IAEA, Vienna (1976) 565.
- [2] Maximum Permissible Body Burdens and Maximum Permissible Concentrations of Radionuclides in Air and in Water for Occupational Exposure; Recommendations of the National Committee on Radiation Exposure, NCRP report no. 22. (National Bureau of Standards Handbook 69) (1959).

TABLE I

CRITERIA FOR SELECTION OF CASES FOR LONG-TERM
MEDICAL FOLLOW-UP²

<u>Condition</u>	<u>Criteria</u>
1. Dose to Whole Body, Active Blood-Forming Organs or Gonads	25 Rem
2. Dose to Skin of Whole Body or Extremities	600 Rem
3. Dose to Other Tissues or Organs from External Source	75 Rem
4. Internal Burdens	1/2 NCRP [2] Maximum Organ Burden
5. Medical Misadministration	All misadministrations, provided they also result in a dose (if a radiation source) or a burden (if a radiopharmaceutical), equal to or greater than the criteria for conditions 1, 2, 3, or 4 above.

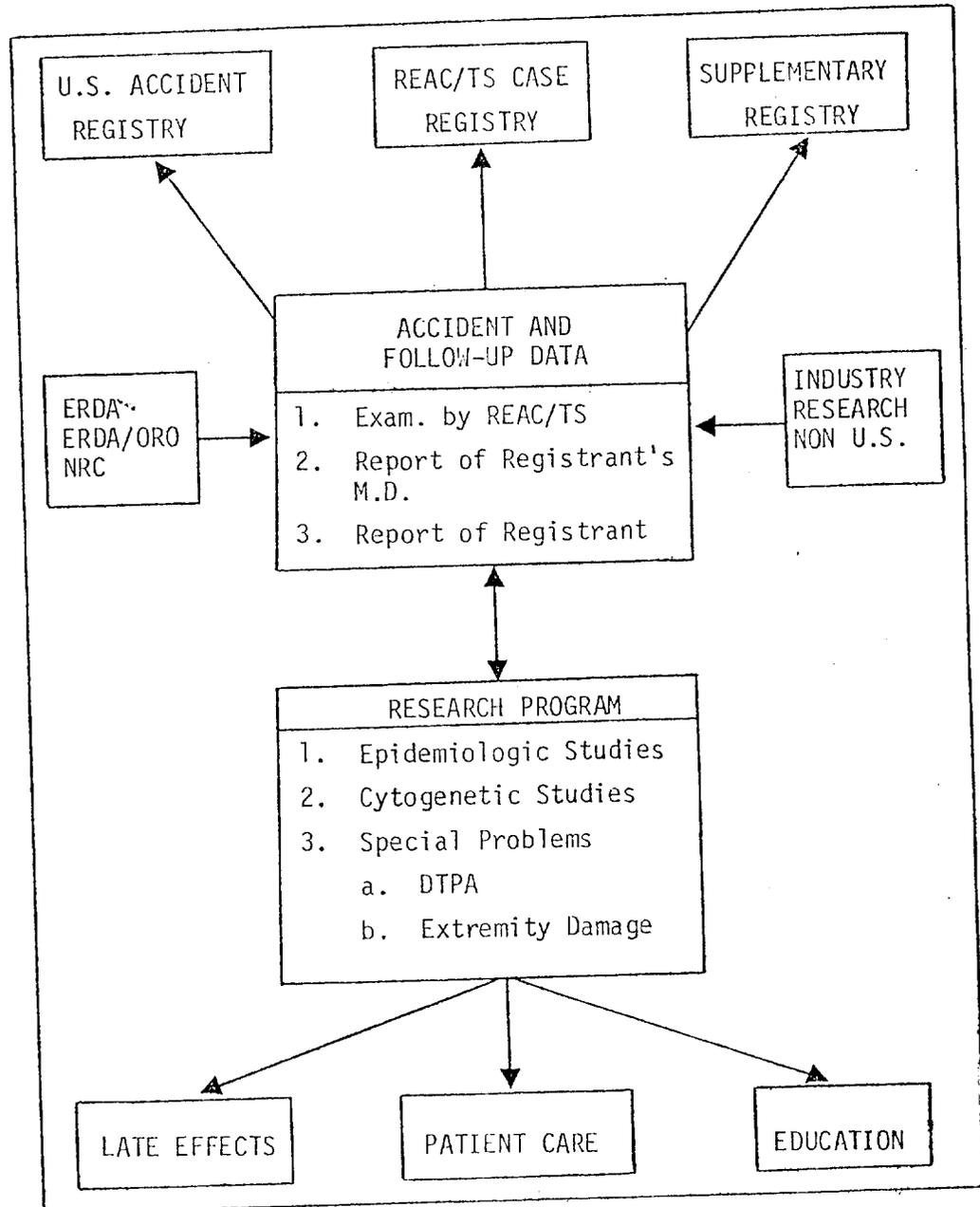
²Agreement between directorate of Regulatory Operations (NRC) and Division of Biomedical & Environmental Research (ERDA) regarding long-term medical follow-up of significant exposures.

FIGURES

Figure 1 REAC/TS Registries

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FIGURE 1
REAC/TS REGISTRIES



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