## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Agency for Toxic Substances and Disease Registry

**[ATSDR–105]**

### Identification of Priority Data Needs for 12 Priority Hazardous Substances

**AGENCY:** Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services (HHS).

**ACTION:** Request for Public Comments on the Identification of Priority Data Needs for 12 Priority Hazardous Substances, and an Ongoing Call for Voluntary Research Proposals.

**SUMMARY:** This Notice makes available for public comment the priority data needs for 12 priority hazardous substances as part of the continuing development and implementation of the ATSDR Substance-Specific Applied Research Program (SSARP). The Notice also serves as a continuous call for voluntary research proposals.
The SSARP is authorized by the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA, and amended by the Superfund Amendments and Reauthorization Act of 1986 (SARA) (42 U.S.C. 9604(i)). This research program was initiated on October 17, 1991. At that time, a list of priority data needs for 38 priority hazardous substances was announced in the Federal Register (56 FR 52178). The list was subsequently revised based on public comments and published in final form on November 16, 1992 (57 FR 54150).

Twelve substances constitute the second list of hazardous substances for which priority data needs are identified by ATSDR. In developing this list, ATSDR solicited input from the Environmental Protection Agency (EPA) and the National Institute of Environmental Health Sciences (NIEHS). The priority data needs documents are available for review by writing to the ATSDR (see **ADDRESSES** section of this Notice).

The exposure and toxicity priority data needs in this Notice have been identified from information gaps via a ''Decision Guide'' that was published in the Federal Register on September 11, 1989 (54 FR 37618). The priority data needs represent essential information to improve the database to conduct public health assessments. Research to address these data needs will help determine the types or levels of exposure that may present significant risks of adverse health effects in people exposed to the subject substances.

The priority data needs identified in this Notice reflect the opinion of the agency, in consultation with other Federal programs, of the research needed pursuant to ATSDR's authority under CERCLA. They do not represent the priority data needs for any other program.

Consistent with section 104(i)(12) of CERCLA as amended (42 U.S.C. 9604(i)(12)), nothing in this research program shall be construed to delay or otherwise affect or impair the authority of the President, the Administrator of ATSDR, or the Administrator of EPA to exercise any authority regarding any other provision of law, including the Toxic Substances Control Act of 1976 (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act of 1972 (FIFRA), or the response and abatement authorities of CERCLA.

In developing this research program, ATSDR has worked with other Federal programs to determine common substance-specific data needs, as well as mechanisms to implement research that may include authorities under TSCA and FIFRA, private-sector voluntarism, or the direct use of CERCLA funds.

When deciding the type of research that should be done, ATSDR considers the recommendations of the Interagency Testing Committee established under section 4(e) of TSCA. Federally funded projects that collect information from 10 or more respondents and are funded by cooperative agreement are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act. If the proposed project involves research on human subjects, the applicants must comply with Department of Health and Human Services Regulations (45 CFR part 46) regarding the protection of human subjects. Assurance must be provided that the project will be subject to initial and continuing review by the appropriate institutional review committees. Overall, data generated from this research program will lend support to others involved in human health assessments involving these 12 substances (and related ones) by providing additional scientific information for the risk assessment process.

The 12 substances, which are included in the ATSDR Priority List of Hazardous Substances established by ATSDR and EPA (59 FR 9486, February 28, 1994), are:

* chlordane
* 1,2-dibromo-3-chloropropane
* di-n-butyl phthalate
* disulfoton
* endrin (includes endrin aldehyde)
* endosulfan (alpha-, beta-, and endosulfan sulfate)
* heptachlor (includes heptachlor epoxide)
* hexachlorobutadiene
* hexachlorocyclohexane (alpha-, beta-, delta-, and gamma-)
* manganese
* methoxychlor
* toxaphene.

The priority data needs for these 12 substances are presented below. We invite comments from the public on individual data needs. After considering the comments, ATSDR will publish the final priority data needs for each substance. These priority data needs will be addressed by the mechanisms described in the ''Implementation of Substance-Specific Applied Research Program'' section of this Federal Register Notice.

This Notice also serves as a continuous call for voluntary research proposals. Private-sector organizations may volunteer to conduct research to address specific priority data needs in this Notice by indicating their interest through submission of a research proposal to ATSDR (see **ADDRESSES** section of this Notice). A Tri-Agency Superfund Applied Research Committee (TASARC) comprised of scientists from ATSDR, the National Toxicology Program (NTP), and EPA will review all proposals.

The substance-specific priority data needs were based on, and determined from, information in corresponding ATSDR toxicological profiles. Background technical information and justification for the priority data needs in this Notice are in the priority data needs documents. These documents are available for review by writing to ATSDR (see **ADDRESSES** section of this Notice).

**DATES:** Comments concerning this Notice must be received by July 1, 1996.

**ADDRESSES:** Include the docket control number ATSDR–42 with comments on this Notice. Submit comments to Dr. William Cibulas, Chief, Research Implementation Branch, Division of Toxicology, ATSDR, 1600 Clifton Road, N.E., Mailstop E–29, Atlanta, Georgia 30333. Use the same address for requests for priority data needs documents and submission of proposals to conduct voluntary research.

Comments on this Notice will be available for public inspection at ATSDR, Building 4, Suite 2400, Executive Park Drive, Atlanta, Georgia (not a mailing address), from 8 a.m. to 4:30 p.m., Monday through Friday, except for legal holidays.

**FOR FURTHER INFORMATION CONTACT:** Dr. William Cibulas, Chief, Research Implementation Branch, Division of Toxicology, ATSDR, 1600 Clifton Road, N.E., Mailstop E–29, Atlanta, Georgia 30333, telephone 404–639–6306.

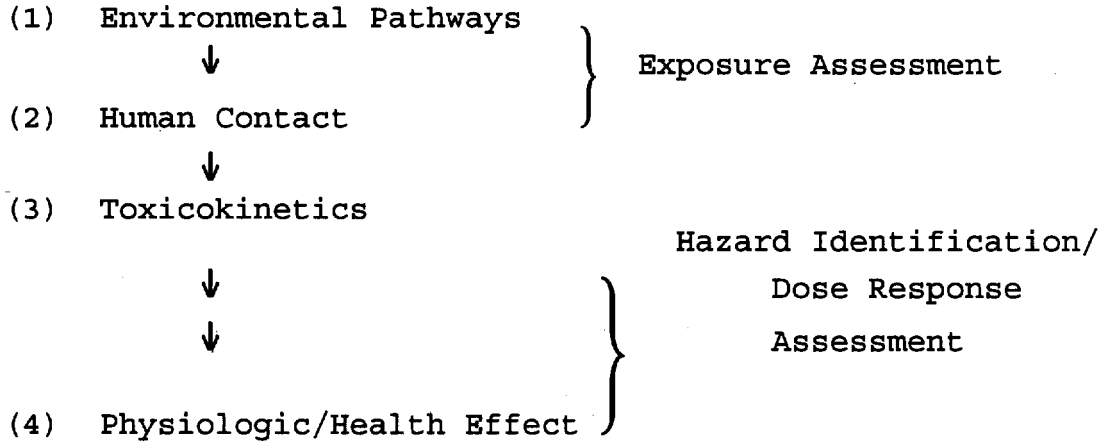
**SUPPLEMENTARY INFORMATION:**

Background

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA (42 U.S.C. 9604 (i)), as amended by the Superfund Amendments and Reauthorization Act of 1986 (SARA) (42 U.S.C. 9604(i)), requires that ATSDR (1) develop jointly with EPA a list of hazardous substances found at National Priorities List (NPL) sites (in order of priority), (2) prepare toxicological profiles of these substances, and (3) assure the initiation of a research program to address identified priority data needs associated with the substances.

The Substance-Specific Applied Research Program was initiated on October 17, 1991. At that time, a list of priority data needs for 38 priority hazardous substances was announced in the Federal Register (56 FR 52178). The list was subsequently revised based on public comments and published in final form on November 16, 1992 (57 FR 54150).

This ATSDR SSARP supplies necessary information to improve the database to conduct public health assessments. This link between research and public health assessments, and the process for distilling priority data needs for ranked hazardous substances from information gaps found in associated ATSDR toxicological profiles, are described in the ATSDR ''Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles'' (54 FR 37618, September 11, 1989). Briefly, this guide identified categories of exposure and toxicity data needs necessary to assess the four basic steps to perform public health assessments.




The links between the release of a hazardous substance in the environment and the impact on human health can only be fully determined when the scientific underpinnings for these four basic steps are known. In the absence of these data, the public health assessment process must use certain assumptions. The relationships between these four steps and priority data needs are as follows:

*Exposure Assessment*

To meet its statutory mandates, ATSDR must make reasonable scientific assessments based on levels of contaminants found in the environment around CERCLA sites. To accomplish this goal, a major objective of this research program is to establish links between levels of contaminants in the environment and levels in human tissues or target organs that may cause an adverse health effect. This requires (1) the development and validation of sensitive analytical methods for measuring levels of contaminants in environmental media, (2) information on background levels in the general environment, (3) information on contaminant levels at or near hazardous waste sites, and (4) knowledge of the contaminants' environmental fate.

Relating environmental contaminant levels to human tissue concentrations requires (1) the development and validation of sensitive analytical methods for contaminant detection in human tissues, (2) bioavailability data, (3) information on background levels in nonexposed populations, and (4) information on levels in tissues for populations living at or near hazardous waste sites. Thus, a major priority data need for this applied research program will be to collect, evaluate, and interpret data from hazardous waste sites for both environmental media and human tissues, when appropriate.

*Hazard Identification/Dose Response Assessment*

Toxicologic and pharmacokinetic testing of priority hazardous substances is necessary to identify target organs and to establish tissue dosimetry. This information is critical to complete the association among levels of these substances in the environment, levels in human tissues, and levels associated with adverse health effects. Priority data needs generally arise when information is lacking that identifies the most sensitive target organs (and doses associated with these effects) following acute, intermediate, and chronic exposures to each substance. These data are needed to establish dose-response relationships, identify thresholds for these effects, and to determine levels of significant exposure to the hazardous substances that are associated with adverse health effects.

The identified health effect studies are conducted via the most relevant exposure route(s) representative of conditions at hazardous waste sites. ATSDR will consider using physiologically based pharmacokinetic (PBPK) modeling to address data needs when models are well developed and validated.

Once links have been established across exposure routes, levels in the environment, and in specific human tissues associated with health effects, it should be feasible to develop strategies to lessen these effects. Mechanistic studies can elucidate the pathophysiology of the health effects

and should ultimately lead to the development of clinical methods to mitigate any adverse health effects from exposure to people living around hazardous waste sites.

ATSDR scientists believe it is important to collect quality human data to validate the substance-specific exposure and toxicity findings from animal studies and equivocal human studies. This information will come from exposure and health effects studies and through the establishment of subregistries within the framework of ATSDR's National Exposure Registry.

## Implementation of Substance-Specific Applied Research Program

In section 104(i)(5)(D), CERCLA states that it is the sense of Congress that the costs for conducting this research program be borne by the manufacturers and processors of the hazardous substances under TSCA and by registrants under the Federal Insecticide, Fungicide, and Rodenticide Act of 1972 (FIFRA), or by cost recovery from responsible parties under CERCLA. To execute this statutory intent, ATSDR developed a plan whereby parts of the SSARP are being conducted via regulatory mechanisms (TSCA/FIFRA), private-sector voluntarism, and through the direct use of CERCLA funds.

CERCLA also requires that ATSDR consider recommendations of the Interagency Testing Committee (ITC) established under section 4(e) of TSCA on the types of research to be done. ATSDR actively participates on this committee; however, none of the proposed 12 substances are now on the ITC priority testing list.

The mechanisms for implementing the SSARP are discussed below. The status of the SSARP in addressing priority data needs of the first set of 38 priority hazardous substances via these mechanisms was described in a Federal Register Notice on March 10, 1994 (59 FR 11434). This will be updated in an upcoming Federal Register Notice.

### *A. TSCA/FIFRA*

In developing and implementing the SSARP, ATSDR and EPA established procedures to identify priority data needs of mutual interest to Federal programs. Generally, this begins before or during the finalization of the priority data needs. These data needs will be addressed through a program of toxicologic testing under TSCA or FIFRA. This part of the research will be conducted according to established TSCA/FIFRA procedures and guidelines. Generally, this testing will fulfill more than one Federal program's need.

### *B. Private-Sector Voluntarism*

As part of the SSARP, on February 7, 1992, ATSDR announced a set of proposed procedures for conducting voluntary research (56 FR 4758). Revisions based on public comments were published on November 16, 1992 (57 FR 54160). ATSDR strongly encourages private-sector organizations to propose research to address data needs at any time until ATSDR announces that research has already been initiated for a specific data need. Private-sector organizations may volunteer to conduct research to address specific priority data needs identified in this Notice by indicating their interest through submission of a research proposal.

The research proposal should be a brief statement (1–2 pages) that addresses the priority data need(s) to be filled, and the methods to be used. The TASARC will review these proposals. Based on the review committee's recommendations, ATSDR will determine which specific voluntary research projects will be pursued (and how) with the volunteer organizations. ATSDR will enter into only those voluntary research projects that lead to high quality, peer-reviewed scientific work. Additional details regarding the process for voluntary research are in the Federal Register Notices cited in this section.

### *C. CERCLA*

Those priority data needs that are not addressed by TSCA/FIFRA or initial voluntarism will be considered for funding by ATSDR through its CERCLA budget. A large part of this research program is envisioned to be unique to CERCLA, for example, research on substances not regulated by other programs or research needs specific to public health assessments. Current examples of the direct use of CERCLA funds include interagency agreements with other Federal agencies and cooperative agreements and grants with academic institutions.

Mechanisms to address these priority data needs may include a second call for voluntarism. Again, scientific peer review of study protocols and results would occur for all research conducted under this auspice.

## Substance-Specific Priority Data Needs

The priority data needs are identified in Table 1. Unique identification numbers (25A through 36H) are assigned to the priority data needs for this list of 12 priority hazardous substances; the initial list of 38 substances has identification numbers 1A through 24C (59 FR 11434, March 10, 1994).

As previously stated, ATSDR believes that part of this research will be most appropriately conducted using CERCLA data and resources. Toward this end, ATSDR has identified particular data needs that may be implemented by ATSDR programs. These priority data needs fall into both the exposure and toxicity data needs categories.

A major exposure priority data need for all 12 substances will be to collect, evaluate, and interpret data from contaminated media around hazardous waste sites. However, a substantial amount of this information has already been collected through individual State programs and the EPA's CERCLA activities. ATSDR scientists will, therefore, evaluate the extant information from these programs in order to better characterize the need for additional site-specific information.

ATSDR's role as a public health agency addressing environmental health is, when appropriate, to collect human data to validate substance-specific exposure and toxicity findings. ATSDR will obtain this information by conducting exposure and health effects studies, and by establishing and using substance-specific subregistries of people enrolled in the agency's National Exposure Registry who are potentially exposed to these substances. When a subregistry or a human exposure study is identified as a priority data need, the responsible ATSDR program will determine its feasibility which depends on identifying appropriate populations and funding. These priority data needs may be reclassified following considerations of feasibility. Any reclassification will be published in the Federal Register.

ATSDR acknowledges that the conduct of human studies to determine possible links between exposure to hazardous substances and human health effects may be accomplished other than by agency programs or under other ATSDR-sponsored projects. We encourage private-sector organizations and other governmental programs to use ATSDR's priority data needs to plan their research activities, including identifying appropriate populations and conducting studies to answer specific human health questions.

Dated: March 26, 1996.

Claire V. Broome,

*Deputy Administrator, Agency for Toxic Substances and Disease Registry.*

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# Table 1
# Substance-Specific Priority Data Needs (PDN) for 12 Priority Hazardous Substances

| Substance | | PDN ID | Priority Data Need |
|---|---|---|---|
| Hexachlorobutadiene | Exposure | 25A | Evaluate existing data on concentrations of hexachlorobutadiene in contaminated environmental media at hazardous waste sites |
| | | 25B | Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers |
| | | 25C | Environmental fate studies that determine the extent to which hexachlorobutadiene volatilizes from soil, and studies that determine the reactions and rates which drive degradation in soil |
| | | 25D | Bioavailability studies in soil and plants |
| | | 25E | Potential candidate for subregistry of exposed persons |
| | Toxicity | 25F | Dose-response data in animals for acute-duration exposure via the oral route |
| Chlordane | Exposure | 26A | Evaluate existing data on concentrations of chlordane in contaminated environmental media at hazardous waste sites |
| | | 26B | Exposure levels in humans living near hazardous waste sites and other populations potentially exposed to chlordane |
| | | 26C | Bioavailability studies following ingestion of contaminated media |
| | | 26D | Potential candidate for subregistry of exposed persons |
| | Toxicity | 26E | Oral multigenerational studies to evaluate reproductive toxicity |

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| Hexachlorocyclohexane α<br>Hexachlorocyclohexane β<br>Hexachlorocyclohexane δ<br>Hexachlorocyclohexane γ | Exposure | 27A | Evaluate existing data on concentrations of HCH in contaminated environmental media at hazardous waste sites |
| | | 27B | Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers |
| | | 27C | Potential candidate for subregistry of exposed persons |
| | Toxicity | 27D | Dose-response data for chronic-duration oral exposure |
| | | 27E | Mechanistic studies on the neurotoxicity, hepatotoxicity, reproductive toxicity and immunotoxicity of hexachlorocyclohexane |
| Heptachlor<br>Heptachlor epoxide | Exposure | 28A | Evaluate existing data on concentrations of heptachlor/heptachlor epoxide in contaminated environmental media at hazardous waste sites |
| | | 28B | Exposure levels in humans living near hazardous waste sites and other populations such as exposed workers |
| | | 28C | Bioavailability from contaminated air, water, and soil and bioaccumulation potential |
| | | 28D | Potential candidate for subregistry of exposed persons |
| | Toxicity | 28E | Dose-response animal data for acute- and intermediate-duration oral exposures, including immunopathology |
| | | 28F | Multigeneration reproductive toxicity studies via the oral route of exposure |
| | | 28G | 2-species developmental toxicity studies via the oral route of exposure |

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| Di-n-butyl phthalate | Exposure | 29A | Evaluate existing data on the concentration of di-n-butyl phthalate in contaminated environmental media at hazardous waste sites |
| | | 29B | Exposure levels in humans living near hazardous waste sites, and other populations such as exposed workers |
| | | 29C | Environmental fate of di-n-butyl phthalate in environmental media |
| | | 29D | Bioavailability in contaminated environmental media near hazardous waste sites |
| | | 29E | Potential candidate for subregistry of exposed persons |
| | Toxicity | 29F | Dose-response data in animals for acute duration exposure via the oral route |
| | | 29G | Dose-response data in animals for chronic duration exposure via the oral route |
| | | 29H | Carcinogenicity studies via oral exposure |
| | | 29I | In vivo genotoxicity studies |
| | | 29J | Immunotoxicology studies via oral exposure |
| | | 29K | Neurotoxicity studies via oral exposure |
| Toxaphene | Exposure | 30A | Exposure levels in humans living in areas near hazardous waste sites with toxaphene and in those individuals with the potential to ingest it |
| | | 30B | Evaluate existing data on concentrations of toxaphene in contaminated environmental media, particularly at hazardous waste sites |
| | | 30C | Potential candidate for subregistry of exposed persons |
| | Toxicity | 30D | Identify the long-term health consequences of exposure to environmental toxaphene via oral exposure |
| | | 30E | Conduct additional chronic animal immunotoxicity studies via the oral route of exposure |
| | | 30F | Conduct additional chronic animal neurotoxicity studies via the oral route of exposure |

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| Endosulfan<br>Endosulfan α<br>Endosulfan β<br>Endosulfan sulfate | | 31A | Evaluate existing data on concentrations of endosulfan in the environment, particularly hazardous waste sites |
| | | 31B | Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers |
| | | 31C | Data on the bioavailability of endosulfan from soil |
| | | 31D | Potential candidate for subregistry of exposed persons |
| | Toxicity | 31E | Acute-duration oral exposure studies |
| | Toxicity | 31F | Sensitive end point neurologic data on the effects of oral endosulfan exposure |
| Disulfoton | | 32A | Evaluate existing data on concentrations of disulfoton in contaminated environmental media at hazardous waste sites |
| | | 32B | Exposure levels of disulfoton in tissues/fluids for populations living near hazardous waste sites and other populations, such as exposed workers |
| | | 32C | Disulfoton should be considered as a potential candidate for a subregistry of exposed persons. |
| | Toxicity | 32D | Immunotoxicology testing battery following oral exposure. |

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| Endrin<br>Endrin aldehyde | Exposure | 33A | Evaluate existing data on concentration of endrin and its degradation products in contaminated environmental media at hazardous waste sites |
| | | 33B | Exposure levels for endrin and its degradation products in humans living near hazardous waste sites |
| | | 33C | Accurately describe the environmental fate of endrin, including environmental breakdown products and rates, media half-lives, and chemical and physical properties of the breakdown products that help predict mobility and volatility |
| | | 33D | Potential candidate for subregistry of exposed persons |
| | Toxicity | 33E | Dose-response animal data for acute oral exposure to endrin |
| | | 33F | Multigeneration reproductive toxicity studies via oral exposure to endrin |
| | | 33G | Accurately describe the toxicokinetics of endrin and its degradation products and identify the animal species to be used as the most appropriate model for human exposure |
| Manganese | Exposure | 34A | Evaluate existing data on concentrations of manganese in contaminated environmental media at hazardous waste sites |
| | | 34B | Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers |
| | | 34C | Potential candidate for subregistry of exposed persons |
| | | 34D | Relative bioavailability of different manganese compounds and bioavailability of manganese from soil |
| | Toxicity | 34E | Dose-response data for acute- and intermediate-duration oral exposures (the subchronic study should include reproductive histopathology and an evaluation of immunologic parameters including manganese effects on plaque-forming cells (SRBC), surface markers (D4:D8 ratio), and delayed hypersensitivity reactions) |
| | | 34F | Toxicokinetic studies on animals to investigate uptake and absorption, relative uptake of differing manganese compounds, metabolism of manganese, and interaction of manganese with other substances following oral exposure |
| | | 34G | Epidemiological studies on the health effects of manganese (special emphasis end points include neurologic, reproductive, developmental, immunologic, and cancer) |

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| Methoxychlor | Exposure | 35A | Evaluate existing data on concentrations of methoxychlor in contaminated media, particularly at hazardous waste sites |
| | | 35B | Exposure levels of methoxychlor and primary metabolites in humans living near hazardous waste sites and in those individuals with the potential to ingest it |
| | | 35C | Evaluate the fate, transport, and levels of the degradation products of methoxychlor in soil |
| | | 35D | Potential candidate for subregistry of exposed persons. |
| | Toxicity | 35E | Evaluate neurologic effects after long-term low-level oral exposure |
| 1,2 dibromo-3-chloropropane | Exposure | 36A | Evaluate existing data on concentrations of 1,2-dibromo-3-chloropropane in contaminated environmental media at hazardous waste sites |
| | | 36B | Exposure levels in humans living near hazardous waste sites and other exposed populations such as exposed workers |
| | | 36C | Potential candidate for subregistry of exposed persons |
| | Toxicity | 36D | Dose-response data in animals for acute duration exposure via the oral route (including reproductive organ histopathology) |
| | | 36E | Dose-response data in animals for chronic-duration exposure via the oral route (including reproductive organ histopathology) |
| | | 36F | Two-species developmental toxicity study via oral exposure |
| | | 36G | Immunotoxicology testing battery via oral exposure |
| | | 36H | Neurotoxicology testing battery via oral exposure |

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