CHEMICAL MANUFACTURERS ASSOCIATION

March 30, 1994

Dear Vinyl Chloride Research Coordinators:

A calendar to determine your availability to attend the next VCRC meeting is enclosed. A tentative agenda for the meeting also is enclosed.

Dr. Greg Bond anticipates sending me the draft scope of work for the epidemiology study by April 7. I will send you the draft as soon as I receive it.

Two activities recently have been initiated by EPA and ATSDR. Dr. James Knaak informs me that **EPA has commissioned Clement Associates to undertake a risk assessment for vinyl chloride.** Dr. Richard Reitz, formerly of Dow Chemical, has developed a physiologically-based pharmacokinetic model for predicting cancer risk from vinyl chloride exposure. An abstract of his model is enclosed. Dr. Knaak has expressed an interest in inviting Dr. Reitz to discuss his model with the VCRC at its next meeting. As EPA's risk assessment activities for vinyl chloride already are underway, I think we should meet with Dr. Reitz as soon as possible and develop a strategy to work with EPA from the beginning to ensure a scientifically sound risk assessment.

On March 10, the **ATSDR announced various research activities that are underway or are planned for vinyl chloride** and other chemicals. The enclosed Federal Register notice describes those research activities. The ATSDR has three different options to develop research data as described in the background section of the Federal Register notice. The VCRC commissioned Can-Tox to review the ATSDR profile for vinyl chloride last year and a final report from Can-Tox was issued early this year. This report has not been submitted to ATSDR. I will contact Dr. William Cibulas of ATSDR to discuss various research programs underway or planned as described in **Tables 1 and 2 of the Federal Register notice.** It is important for the vinyl chloride industry to meet with ATSDR and/or EPA to discuss the ATSDR data needs because the ultimate cost of the ATSDR data needs on the industry will be well over $500,000, if the data needs are not minimized. One way or the other, industry ultimately will have to pay for all test costs. We will discuss the enclosed Federal Register notice at our next meeting and decide on a course of action.

Please complete your meeting availability calendar and send it to me by fax at 202/887-1237. If you have any questions, please call me at (202) 887-1192.

Sincerely,

Has Shah

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Enclosures

BFG 00201

2501 M Street, NW, Washington, DC 20037 Telephone 202-887-1100 Fax 202-887-1237

CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Panel

Vinyl Chloride Research Coordinators

Tentative Agenda

DATE: TO BE ANNOUNCED

TIME: TO BE ANNOUNCED

PLACE: CMA Offices
2501 M Street, NW
Washington, D.C.

1.0 Approval of February 14, 1994 Record of Meeting

2.0 Discussion of Scope of Work of the Epidemiology Study

3.0 Discussion of Potential Contractors for the Epidemiology Study

4.0 Discussion of Cost Sharing Formula for the Epidemiology Study

5.0 Presentation by Richard Reitz on Predicting Cancer Risk from Vinyl Chloride Exposure with a Physiologically-Based Pharmacokinetic Model - TENTATIVE

6.0 Discussion of Course of Action with EPA on Vinyl Chloride Risk Assessment

7.0 Discussion of ATSDR Research Data Needs for Vinyl Chloride

8.0 Discussion of Course of Action with ATSDR on Its Priority Data Needs

9.0 Financial Statement

10.0 Schedule Date for Next Meeting or Conference Call

Has Shah

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Subject to Approval

SEMINAR TOPIC #1

Predicting Cancer Risk from Vinyl Chloride Exposure with a Physiologically-Based Pharmacokinetic Model.

Richard H. Reitz
McLaren/Hart, ChemRisk Division

Physiologically-based pharmacokinetic (PB -PK) models have been proposed as tools for facilitating the extrapolation of animal cancer tests to humans. For instance, several of us (Reitz, Andersen, Gargas, Clewell) developed a risk assessment for methylene chloride which used PB -PK modeling to extrapolate between species, across different routes of exposure, and from high dose to low dose. This risk assessment predicted considerably less risk to humans than earlier procedures, and the PB-PK risk assessment was consistent with epidemiology studies for methylene chloride (which are generally accepted as negative).

Because the epidemiology studies for methylene chloride are negative (as the PB -PK model predicted they would be), they do not provide an opportunity for comparing cancer rates in humans with predictions derived from the PB -PK model. However, there is one industrial compound (vinyl chloride, VC) which has been shown to produce measurable increases in the incidence of liver angiosarcoma in both rats and humans. In order to determine whether risk assessments based on PB -PK adjustments of dose adjustments are too conservative, not conservative enough, or about right, we have developed a PB -PK model for VC and predicted the risk to humans based on rat studies.

The VC model for rats and humans was developed from several in vivo and in vitro data sets. Both the rat and human models were then validated with independent studies of VC metabolism in the appropriate species (i.e. the validation studies were not used in development of the model itself). Then PB -PK model was combined with the multistage model of Crump & Howe (GLOBAL83) to predict the incidence of liver angiosacroma produced in humans. The human studies included more than 12,000 workers exposed to VC occupationally over a period of several decades.

The risk assessment based on the PB -PK model predicted considerably less risk than would be calculated by default (nonpharmacokinetic) procedures. However, the incidence of angiosarcoma actually observed in human subjects was still considerably lower than predicted by the PB -PK/multistage model, suggesting that if the results obtained with VC are typical, risk assessments combining PB -PK and multistage modeling likely overpredict, rather than underpredict, human risk.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Toxic Substances and Disease Registry

[ATSDR–79]

Status of the Superfund Substance-Specific Applied Research Program

AGENCY: Agency for Toxic Substances and Disease Registry (ATSDR), Public Health Service (PHS), Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: This notice provides the status of ATSDR's effort to implement the Agency's Substance-Specific Applied Research Program (SSARP). This research program, authorized by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), as amended by the Superfund Amendments and Reauthorization Act (SARA) [42 U.S.C. 9604 (i)], was initiated on October 17, 1991. At that time, a list of priority data needs for 38 priority hazardous substanceswas 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).

The 38 substances, each of which is found on ATSDR's "List of Priority Hazardous Substances" (56 FR 52166, October 17, 1991), are aldrin/dieldrin, arsenic, benzene, beryllium, cadmium, carbon tetrachloride, chloroethane, chloroform, chromium, cyanide, p,p'-DDT,DDE,DDD, di(2-ethylhexyl)phthalate, lead, mercury, methylene chloride, nickel, polychlorinated biphenyl compounds (PCBs), polycyclic aromatic hydrocarbons (PAHs) (includes 15 substances), selenium, tetrachloroethylene, toluene, trichloroethylene, vinyl chloride, and zinc.

This notice also serves as a continuous call for voluntary research initiatives. ATSDR encourages private sector organizations to volunteer to conduct research to fill specific priority data needs. A Tri-Agency Superfund Applied Research Committee (TASARC) comprised of scientists from ATSDR, the National Toxicology Program (NTP), and the Environmental Protection Agency (EPA) will review all proposed voluntary research efforts.

DATES: ATSDR considers the voluntary research effort to be important to the continuing development of the SSARP. Therefore, the Agency encourages private sector organizations to volunteer at any time to conduct research to fill identified data needs, until ATSDR announces that research has been initiated for a specific data need.

ADDRESSES: Private sector organizations interested in volunteering to conduct this type of research may write to Dr. William Cibulas, Chief, Research Implementation Branch, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Mailstop E–29, 1600 Clifton Road, NE., Atlanta, Georgia 30333.

FOR FURTHER INFORMATION CONTACT: Dr. William Cibulas, Chief, Research Implementation Branch, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Mailstop E–29, 1600 Clifton Road, NE., Atlanta, Georgia 30333, telephone (404) 639–6306.

SUPPLEMENTARY INFORMATION:

Background

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA, as amended by the Superfund Amendments and Reauthorization Act (SARA) [42 U.S.C. 9604(i)], requires that ATSDR (1) jointly with the Environmental Protection Agency (EPA), develop and prioritize a list of hazardous substances found at National Priorities List (NPL) sites, (2) prepare toxicological profiles for these substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances. Before starting such a program, ATSDR will consider recommendations of the Interagency Testing Committee established under section 4(e) of the Toxic Substances Control Act on the type of research that should be done.

On October 17, 1991, ATSDR announced the identification of the priority data needs for 38 priority hazardous substances (56 FR 52178), requested public comments, and invited private sector organizations to volunteer to conduct research to fill specific priority data needs. On November 16, 1992, the Agency published a revised list of 117 priority data needs for these priority hazardous substances (57 FR 54150).

The major goals of the ATSDR SSARP are: (1) To fill the substance-specific information needs of the public and scientific community, and (2) to supply information necessary to conduct comprehensive public health assessments of populations living near hazardous waste sites. This program also will provide data that can be generalized to other substances or areas of science, including risk assessment of chemicals, thus creating a scientific base for filling a broader range of data needs.

CERCLA, in section 104(i)(5)(D), 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 the Toxic Substances Control Act (TSCA) and by registrants under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), or by cost recovery from responsible parties under CERCLA. To effect this statutory intent, ATSDR developed a plan whereby parts of the SSARP will be conducted via regulatory mechanisms (TSCA/FIFRA), private sector voluntarism, and the direct use of CERCLA funds.

A Tri-Agency Superfund Applied Research Committee (TASARC) comprised of scientists from ATSDR, NTP, and the EPA has been set up to: (1) Advise on the assignment of priorities on mechanisms for filling data needs; (2) coordinate knowledge of research activities to avoid duplication of research in other programs and under other authorities; (3) advise on issues of science related to substance-specific data needs; and (4) maintain a scheduled forum that provides an overall review of the ATSDR SSARP. The TASARC has met four times since the initiation of the SSARP. This notice provides the status of ATSDR's efforts to implement the SSARP, focussing on ongoing activities relevant to test rule development under TSCA/FIFRA, private sector voluntarism, and direct use of CERCLA funds. Additional data needs are being addressed through an interagency agreement with NTP, by ATSDR's Great Lakes human health effects research program, and other Agency programs. To date, 59 priority data needs associated with 35 ATSDR priority hazardous substances (including 15 PAHs) are being addressed via these mechanisms (Table 1).

A. TSCA/FIFRA

In developing and implementing the SSARP, ATSDR, NTP, and EPA have established procedures to identify priority data needs of mutual interest to Federal programs. These data needs will be filled through a program of toxicological testing under TSCA. This portion of the research will be conducted according to established TSCA procedures and guidelines. This testing will fulfill more than one Federal program's need. During FY 1993, a subset of the 117 priority data needs for 38 substances (about 60) was referred to the EPA under its authorities following

review and endorsement by the TASARC oversight committee.

Currently, 26 priority data needs associated with 11 ATSDR substances have been recommended by EPA to be added to its Master Testing List, the first step in test rule development under TSCA, section 4 (Table 2). Please note that although ATSDR has identified priority data needs for oral exposure to tetrachloroethylene, cyanide, and beryllium, in response to other Federal government agency needs, ATSDR will consider proposals to conduct inhalation studies in conjunction with pharmacokinetic studies for these substances in lieu of bioassays using oral exposures. It is anticipated that inhalation data derived from these studies can be used, in conjunction with pharmacokinetic modeling, to address ATSDR's oral toxicity data needs.

Some of ATSDR's priority hazardous substances will not be added to EPA's Master Testing list because they do not fall within the bounds of TSCA, Section 4 authority. For example, TSCA does not require testing chemicals that are out of production, such as PCBs. Furthermore, TSCA is not considered the appropriate mechanism for testing PAHs, because the PAHs are by-products of multiple industrial processes and, therefore, it is difficult to identify specific manufacturers. In addition, TSCA guidelines are not available for some of the ATSDR priority data needs such as the development of analytical methods for cadmium and beryllium, mechanistic studies on the neurotoxic effects of lead, and the mitigation of toxicity of vinyl chloride. Moreover, some of the ATSDR priority hazardous substances are considered more appropriate for FIFRA than TSCA, e.g., arsenic, DDT, and aldrin/dieldrin. The Office of Pollution, Prevention and Toxics (OPPT), EPA, forwarded the data needs for these substances to the Office of Pesticide Programs for evaluation.

B. Private Sector Voluntarism

As part of the SSARP, ATSDR initially announced a set of proposed procedures for conducting voluntary research on February 7, 1992 (56 FR 4758). It was revised based on public comments and published on November 16, 1992 (57 FR 54160). This voluntary research program fills priority data needs along with other mechanisms such as test rule development through EPA and CERCLA-funded research. Private sector organizations were encouraged to volunteer to conduct research to fill these specific priority data needs.

Currently, ATSDR is pursuing voluntary research interests with two private sector organizations: the General Electric Company (GE) and the Halogenated Solvents Industry Alliance (HSIA). To date, through the voluntary research efforts of GE and HSIA, four priority data needs for two substances are under discussion, potentially leading to the signing of two memorandums of understanding (Table 3).

During FY 1993, ATSDR staff members met with officials from GE to discuss the Agency's research agenda for PCBs. The Agency has identified mutual interests in environmental fate testing and human health endpoints assessments and has initiated discussion on these studies with GE.

ATSDR met with HSIA representatives to discuss the use of physiologically-based pharmacokinetic (PBPK) models to fill priority data needs for six volatile organic compounds. The Agency selected methylene chloride to start using PBPK modeling to address ATSDR's toxicity priority data needs because of the extensive database on this substance. The toxicity priority data needs for the remaining 5 volatile organic compounds (carbon tetrachloride, chloroethane, chloroform, tetrachloroethylene, and trichloroethylene) may be addressed via similar voluntary efforts in the future.

C. CERCLA-Funded Research (Minority Health Professions Foundation Research Program)

During FY 1992, ATSDR announced a $4 million cooperative agreement program with the Minority Health Professions Foundation (MHPF) to support substance-specific investigations. This cooperative venture is supported by the direct use of CERCLA funds. During FY 1993, about $4 million was allocated to continue this research program; no new projects were initiated. Currently, 9 priority data needs for 21 priority hazardous substances (including 15 PAHs) in the SSARP are being addressed by the MHPF institutions through this program. Also, the MHPF research program will address 13 other substance-specific data needs identified in the ATSDR toxicological profiles concerning exposures and related health effects. The institutions receiving awards and their respective research projects are listed in Table 4.

The MHPF, a not-for-profit 501(c)(3) organization, is comprised of 11 minority health professions schools. Its primary mission is to research the persistent health problems that disproportionately plague poor and minority citizens. The purposes of the ATSDR-MHPF cooperative agreement are: (1) To initiate research to fill ATSDR-identified data needs for priority hazardous substances, and (2) to enhance existing disciplinary capacities to conduct research in environmental health at MHPF member institutions.

The areas of research at MHPF institutions include those related to broad areas of toxicology and environmental health science. Some of the MHPF member institutions are conducting health studies of minority groups exposed to ATSDR's priority hazardous substances.

D. National Toxicology Program

ATSDR maintains an interagency agreement (IAG) with NTP to conduct toxicological testing of substances identified at NPL sites. The studies determine levels of exposure that present a significant risk to humans of acute, subacute, and chronic health effects. Often these studies include an assessment of the substance's ability to cause cancer, reproductive toxicity, and birth defects. The results of these studies are used by regulatory agencies such as the Food and Drug Administration and the EPA, various environmental and industrial groups, and ATSDR to improve the ability to conduct public health assessments at NPL sites. Under this agreement, one toxicity priority data need identified in the SSARP (carbon tetrachloride, immunotoxicology battery of tests via oral exposure) is currently being addressed. This NTP study was begun in September 1993 and should be completed in February 1994.

E. Great Lakes Human Health Effects Research Program

Some of the priority data needs identified in the SSARP have been independently identified as research needs through the ATSDR Great Lakes human health effects research program, a separate research program. To date, 12 priority data needs for 19 priority hazardous substances (including 15 PAHs) identified in the SSARP are being addressed through this program. The institutions receiving awards and their respective studies are listed in Table 5.

The Great Lakes Critical Programs Act of 1990 mandates EPA, in consultation with ATSDR, to prepare a report by September 30, 1994, that assesses the adverse effects of pollutants in the Great Lakes system on the health of individuals in the Great Lakes states. A variety of persistent toxic substances are prevalent in the Great Lakes, including PCBs, DDT and its metabolites, dieldrin, toxaphene, mirex, mercury,

benzo(a)pyrene, hexachlorobenzene, furans, dioxins, and lead. Certain populations—Native Americans, sport anglers, fetuses and nursing infants of mothers who consume contaminated Great Lakes fish—have a potentially higher risk of long-term adverse effects resulting from exposure to these contaminants.

The ATSDR-supported research projects focus on these high-risk populations to try to further define the human health consequences of exposure to these persistently toxic substances. The research activities include, but are not limited to: (1) Characterizing exposure and determining the profiles and levels of Great Lakes contaminants in biological tissues and fluids in high-risk populations; (2) identifying sensitive and specific human reproductive/developmental end points and correlating them to exposure to Great Lakes contaminants; (3) determining the short- and long-term risk(s) of adverse health effects in progeny whose parents were exposed to Great Lakes contaminants; (4) investigating the feasibility of establishing registries and surveillance cohorts in the Great Lakes region; and (5) establishing a chemical mixtures database with emphasis on tissue and blood levels in order to identify new cohorts, conduct surveillance and health effects studies, and establish registries and surveillance cohorts.

During FY 1992, ATSDR announced a $2 million grant program to conduct research on the impact on human health of contaminated fish consumption in the Great Lakes region. On September 30, 1992, ATSDR announced nine awards under this program.

In FY 1993, about $3 million was allocated to support the continuation of the research projects conducted at the nine institutions originally funded during FY 1992. In addition, ATSDR awarded one new grant to the Michigan Department of Public Health to design, establish, and operate a professionally creditable interlaboratory quality assurance/quality control program for the ATSDR Great Lakes human health effects research program.

F. Other ATSDR Programs

In its role as a public health agency addressing environmental health, ATSDR may, where appropriate, collect human data to validate substance-specific exposure and toxicity findings; information on levels of contaminants in humans has been identified as a priority data need for 37 of the 38 priority substances (Table 1). ATSDR will obtain this information through exposure and health effects studies, and through establishing and using substance-specific subregistries of people within the Agency's National Exposure Registry who have potentially been exposed to these substances.

The list of 38 priority hazardous substances in the SSARP was forwarded to ATSDR's Exposure and Disease Registry Branch (EDRB), Division of Health Studies, for consideration as potential candidates for subregistries of exposed persons, based on criteria described in EDRB's 1988 document, "Policies and Procedures for Establishing a National Registry of Persons Exposed to Hazardous Substances." To date, ATSDR has selected benzene, chromium, and trichloroethylene as primary contaminants to establish subregistries in the National Exposure Registry. However, aldrin/dieldrin, carbon tetrachloride, chloroethane, chloroform, cyanide, p,p'-DDT, DDE, DDD, di (2-ethylhexyl) phthalate, mercury, methylene chloride, PAHs, selenium, tetrachloroethylene, and vinyl chloride remain as a part of the candidate pool. They will be considered for selection as primary contaminants during each selection process (Table 1). Finally, arsenic, beryllium, cadmium, lead, nickel, PCBs, toluene, and zinc are not considered to be in the pool of candidate substances for an exposure registry at this time. This decision will be re-evaluated as more information on the chemicals and exposure sites becomes available.

With regard to epidemiologic studies, ATSDR believes that for many of the 38 priority hazardous substances, an extensive amount of animal data, and some human data, have already been collected; therefore, ATSDR considers it appropriate, where feasible, to conduct epidemiologic studies on such substances. In response to public comments, the Agency's SSARP will address substance-specific rather than site-specific epidemiologic studies.

The substance-specific studies are designed to determine substance-specific cause and effect. In this case, ATSDR is not necessarily directed toward populations exposed via the environment at hazardous substance release sites, as in a site-specific study. Instead, any appropriate population of suitable exposure via the environment, consumer products, or occupation can be used to design a rigorous analytic epidemiologic investigation. Epidemiologic studies on several of ATSDR's 38 priority hazardous substances (such as DDT, PCBs, and PAHs) are being conducted by the ATSDR Great Lakes human health effects research program (Table 5).

Two epidemiologic studies on lead (identified as a data need by ATSDR), are also being conducted by the Morehouse School of Medicine and the King/Drew Medical Center of the Charles R. Drew University of Medicine and Science via the ATSDR—MHPF cooperative agreement. ATSDR expects that other substance-specific epidemiologic studies, identified as data needs or priority data needs in the SSARP, may potentially be conducted by other Divisions within ATSDR.

ATSDR acknowledges that the conduct of epidemiologic studies to determine possible linkages between exposure to hazardous substances and human health effects may be accomplished other than by Agency programs, or under other ATSDR-sponsored auspices. Toward that end, the Agency encourages the private sector and other government programs to use ATSDR's priority data needs to plan research activities to identify appropriate populations and conduct studies addressing the specific human health issues.

Finally, the collection, evaluation, and interpretation of data from contaminated media around hazardous waste sites have been identified as priority data needs for all 38 priority hazardous substances by ATSDR. However, the Agency realizes that a lot of information has already been collected through individual state programs and the EPA's CERCLA activities; therefore, ATSDR will evaluate the extant information from these programs in order to help fill data needs on substance-specific exposures.

The results of the research conducted via the SSARP will be used for public health assessments and to reassess ATSDR's substance-specific priority data needs. The Agency expects to re-evaluate the priority data needs for priority hazardous substances every three years.

Dated: March 3, 1994.

Walter R. Dowdle,

Deputy Administrator, Agency for Toxic Substances and Disease Registry.

TABLE 1.—SUBSTANCE-SPECIFIC PRIORITY DATA NEEDS CURRENTLY BEING ADDRESSED UNDER ATSDR'S APPLIED RESEARCH PROGRAMS

	Substance	ID	Priority Data Need	Addressed
	Lead	1A	Mechanistic studies on the neurotoxic effects of lead	✔
		1B	Analytical methods for tissue levels	
		1C	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	✔
✓	Arsenic	2A	Comparative toxicokinetic studies to determine if an appropriate animal species can be identified.	
		2B	Half-lives in surface water, groundwater	
		2C	Bioavailability from soil	
		2D	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
	Mercury	3A	Multigeneration reproductive toxicity study via oral exposure	✔
		3B	Dose-response data in animals for chronic-duration oral exposure	✔
		3C	Immunotoxicology battery of tests via oral exposure	✔
		3D	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	✔
		3E	Potential candidate for subregistry of exposed persons	✔
✓	Vinyl Chloride	4A	Dose-response data in animals for acute-duration inhalation exposure	
		4B	Multigeneration reproductive toxicity study via inhalation	✔
		4C	Dose-response data in animals for chronic-duration inhalation exposure	
		4D	Mitigation of vinyl chloride-induced toxicity	
		4E	2-species developmental toxicity study via inhalation	✔
		4F	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
		4G	Potential candidate for subregistry of exposed persons	✔
✓	Benzene	5A	Dose-response data in animals for acute- and intermediate-duration oral exposure. The subchronic study should include an extended reproductive organ histopathology.	✔
		5B	2-species developmental toxicity study via oral exposure	✔
		5C	Neurotoxicology battery of tests via oral exposure	✔
		5D	Epidemiological studies on the health effects of benzene (Special emphasis endpoints include: immunotoxicity).	
		5E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
	Cadmium	6A	Analytical methods for biological tissues and fluids and environmental media	
		6B	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
✓	PCBs	7A	Dose-response data in animals for acute- and intermediate-duration oral exposures	✔
		7B	Biodegradation of PCBs in water; bioavailability of PCBs in air, water and soil	✔
		7C	Dose-response data in animals for acute- and intermediate-duration inhalation exposures. The subchronic study should include extended reproductive organ histopathology.	
		7D	Epidemiological studies on the health effects of PCBs (Special emphasis endpoints include: immunotoxicity, gastrointestinal toxicity, liver, kidney, thyroid toxicity, reproductive/developmental toxicity).	✔
		7E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	✔
	Chloroform	8A	Dose-response data in animals for intermediate-duration oral exposure	
		8B	Epidemiological studies on the health effects of chloroform (Special emphasis endpoints include: cancer, neurotoxicity, reproductive and developmental toxicity, hepatotoxicity, and renal toxicity).	
		8C	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
		8D	Potential candidate for subregistry of exposed persons	✔
	PAHs	9A	Dose-response data in animals for intermediate duration oral exposures. The subchronic study should include extended reproductive organ histopathology and immunopathology.	✔
		9B	2-species developmental toxicity study via inhalation or oral exposure	
		9C	Mechanistic studies on PAHs, on how mixtures of PAHs can influence the ultimate activation of PAHs, and on how PAHs affect rapidly proliferating tissues.	
		9D	Dose-response data in animals for acute- and intermediate-duration inhalation exposures. The subchronic study should include extended reproductive organ histopathology and immunopathology.	✔
		9E	Epidemiological studies on the health effects of PAHs (Special emphasis endpoints include: cancer, dermal, hemolymphatic, and hepatic).	✔
		9F	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	✔
		9G	Potential candidate for subregistry of exposed persons	✔
	Trichloroethylene	10A	Dose-response data in animals for acute-duration oral exposure	✔
		10B	Neurotoxicology battery of tests via the oral route	✔
		10C	Immunotoxicology battery of tests via the oral route	✔
		10D	Epidemiological studies on the health effects of trichloroethylene (Special emphasis endpoints include: cancer, hepatotoxicity, renal toxicity, developmental toxicity, and neurotoxicity).	

TABLE 1.—SUBSTANCE-SPECIFIC PRIORITY DATA NEEDS CURRENTLY BEING ADDRESSED UNDER ATSDR'S APPLIED RESEARCH PROGRAMS—Continued

	Substance	ID	Priority Data Need	Addressed
		10E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
	DDT	11A	Dose-response data in animals for chronic-duration oral exposure	
		11B	Comparative toxicokinetic study (across routes/species)	
		11C	Bioavailability and bioaccumulation from soil	
		11D	Epidemiological studies on the health effects of DDT, DDD and DDE (Special emphasis endpoints include: immunotoxicity, reproductive and developmental toxicity).	✔
		11E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	✔
		11F	Potential candidate for subregistry of exposed persons	✔
✓	Chromium	12A	Dose-response data in animals for acute-duration exposure to chromium (VI) and (III) via oral exposure and for intermediate-duration exposure to chromium (VI) via oral exposure.	✔
		12B	Multigeneration reproductive toxicity study via oral exposure to chromium (III) and (VI)	✔
		12C	Immunotoxicology battery of tests following oral exposure to chromium (III) and (VI)	✔
		12D	2-species developmental toxicity study via oral exposure to chromium (III) and (VI)	
		12E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
	Tetrachloroethylene	13A	Dose-response data in animals for acute-duration oral exposure, including neuropathology and demeanor, and immunopathology.	✔
		13B	Multigeneration reproductive toxicity study via oral exposure	✔
		13C	Dose-response data in animals for chronic-duration oral exposure, including neuropathology and demeanor, and immunopathology.	
		13D	2-species developmental toxicity study via oral exposure	✔
		13E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
		13F	Potential candidate for subregistry of exposed persons	✔
	Aldrin/Dieldrin	14A	Dose-response data in animals for intermediate-duration oral exposure	
		14B	Bioavailability from soil	
		14C	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
		14D	Potential candidate for subregistry of exposed persons	✔
	Cyanide	15A	Dose-response data in animals for acute- and intermediate-duration exposures via inhalation. The subchronic study should include extended reproductive organ histopathology and evaluation of neurobehavioral and neuropathological endpoints.	✔
		15B	2-species developmental toxicity study via oral exposure	✔
		15C	Evaluation of the environmental fate of cyanide in soil	✔
		15D	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
		15E	Potential candidate for subregistry of exposed persons	✔
	Carbon Tetrachloride	16A	Dose-response data in animals for chronic oral exposure. The study should include extended reproductive organ and nervous tissue (and demeanor) histopathology.	
		16B	Immunotoxicology battery of tests via oral exposure	✔
		16C	Half-life in soil	
		16D	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
		16E	Potential candidate for subregistry of exposed persons	✔
	Beryllium	17A	Dose-response data in animals for acute- and intermediate-duration inhalation exposures. The subchronic study should include extended reproductive organ histopathology.	✔
		17B	2-species developmental toxicity study via inhalation exposure	✔
		17C	Environmental fate in air; factors affecting bioavailability in air	✔
		17D	Analytical methods to determine environmental speciation	
		17E	Immunotoxicology battery of tests following oral exposure	✔
		17F	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
	Toluene	18A	Dose-response data in animals for acute- and intermediate-duration oral exposures. The subchronic study should include an extended histopathological evaluation of the immune system.	✔
		18B	Comparative toxicokinetic studies (Characterization of absorption, distribution, and excretion via oral exposure).	✔
		18C	Neurotoxicology battery of tests via oral exposure	✔
		18D	Mechanism of toluene-induced neurotoxicity	
		18E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
✓	Nickel	19A	Epidemiological studies on the health effects of nickel (Special emphasis endpoints include: reproductive toxicity).	
		19B	2-species developmental toxicity study via the oral route	
		19C	Dose-response data in animals for acute- and intermediate-duration oral exposures	
		19D	Neurotoxicology battery of tests via oral exposure	
		19E	Bioavailability of nickel from soil	
		19F	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	

TABLE 1.—SUBSTANCE-SPECIFIC PRIORITY DATA NEEDS CURRENTLY BEING ADDRESSED UNDER ATSDR'S APPLIED RESEARCH PROGRAMS—Continued

Substance	ID	Priority Data Need	Addressed
Methylene Chloride	20A	Dose-response data in animals for acute- and intermediate-duration oral exposure. The subchronic study should include extended reproductive organ histopathology, neuropathology and demeanor, and immunopathology.	✔
	20B	2-species developmental toxicity study via the oral route	✔
	20C	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
	20D	Potential candidate for subregistry of exposed persons	✔
Zinc	21A	Dose-response data in animals for acute- and intermediate-duration oral exposures. The subchronic study should include an extended histopathological evaluation of the immunologic and neurological systems.	✔
	21B	Multigeneration reproductive toxicity study via oral exposure	
	21C	Carcinogenicity testing (2-year bioassay) via oral exposure	
	21D	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
✔ DEHP	22A	Epidemiological studies on the health effects of DEHP (Special emphasis endpoints include: cancer).	
	22B	Dose-response data in animals for acute- and intermediate-duration oral exposures. The subchronic study should include an extended histopathological evaluation of the immunologic and neurologic systems.	
	22C	Multigeneration reproductive toxicity study via oral exposure	
	22D	Comparative toxicokinetic studies (Studies designed to examine how primates metabolize and distribute DEHP as compared to rodents via oral exposure).	✔
	22E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
	22F	Potential candidate for subregistry of exposed persons	✔
Selenium	23A	Dose-response data in animals for acute-duration oral exposure	
	23B	Immunotoxicology battery of tests via oral exposure	
	23C	Epidemiological studies on the health effects of selenium (Special emphasis endpoints include: cancer, reproductive and developmental toxicity, hepatotoxicity and adverse skin effects).	
	23D	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	
	23E	Potential candidate for subregistry of exposed persons	✔
Chloroethane	24A	Dose-response data in animals for acute- and intermediate-duration oral exposures. The subchronic study should include an evaluation of immune and nervous system (and behavior, demeanor) tissues, and extended reproductive organ histopathology.	✔
	24B	Dose-response data in animals for chronic inhalation exposures. The study should include an evaluation of nervous system (and behavior) tissues.	
	24C	Potential candidate for subregistry of exposed persons	✔

*These substances are included in the pool of candidate substances for subregistry development. These substances will be considered for selection as primary contaminants by the Division of Health Studies, ATSDR, during each selection process.

TABLE 2.—PRIORITY DATA NEEDS BEING ADDRESSED BY EPA RULE MAKING

Substance	ID	Priority Data Need	TSCA/FIFRA
Mercury	3B	Dose-response data in animals for chronic-duration oral exposure	TSCA.
	3C	Immunotoxicology battery of tests via oral exposure	TSCA.
✔ Vinyl Chloride	4B	Multigeneration reproductive toxicity study via inhalation	TSCA.
	4D	2-species developmental toxicity study via inhalation	TSCA.
✔ Benzene	5A	Dose-response data in animals for intermediate-duration oral exposure. The subchronic study should include an extended reproductive organ histopathology.	TSCA.
	5C	Neurotoxicology battery of tests via oral exposure	TSCA.
Trichloroethylene	10A	Dose-response data in animals for acute-duration oral exposure	TSCA.
	10C	Immunotoxicology battery of tests via the oral route	TSCA.
✔ Chromium	12A	Dose-response data in animals for acute-duration exposure to chromium(VI) and (III) via oral exposure.	TSCA.
	12B	Multigeneration reproductive toxicity study via oral exposure to chromium (III) and (VI).	TSCA.
	12C	Immunotoxicology battery of tests following oral exposure to chromium (III) and (VI)	TSCA.
Tetrachloroethylene	13A	Dose-response data in animals for acute-duration oral exposure, including neuropathology and demeanor, and immunopathology.	TSCA (inhalation study).
	13B	Multigeneration reproductive toxicity study via oral exposure	TSCA (inhalation study).
	13D	2-Species developmental toxicity study via oral exposure	TSCA (inhalation study).

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TABLE 2.—PRIORITY DATA NEEDS BEING ADDRESSED BY EPA RULE MAKING—Continued

Substance	ID	Priority Data Need	TSCA/FIFRA
Cyanide	15A	Dose-response data in animals for acute- and intermediate-duration exposures via inhalation. The subacute study should include extended reproductive organ histopathology and evaluation of neurobehavioral and neuropathological endpoints.	TSCA.
	15B	2-Species developmental toxicity study via oral exposure	TSCA (inhalation study).
	15C	Evaluation of the environmental fate of cyanide in soil	TSCA.
Beryllium	17A	Dose-response data in animals for acute- and intermediate-duration inhalation exposures. The subchronic study should include extended reproductive organ histopathology.	TSCA.
	17B	2-species developmental toxicity study via inhalation exposure	TSCA.
	17C	Environmental fate in air; factors affecting bioavailability in air	TSCA.
	17E	Immunotoxicology battery of tests following oral exposure	TSCA (inhalation study).
Toluene	18A	Dose-response data in animals for intermediateduration oral exposures. The study should include an extended histopathological evaluation of the immune system.	TSCA.
	18B	Comparative toxicokinetic studies (Characterization of absorption, distribution, and excretion via oral exposure).	TSCA.
Methylene Chloride	20A	Dose-response data in animals for intermediate-duration oral exposure. The study should include extended immunopathology and neuropathology.	TSCA.
	20B	2-species developmental toxicity study via the oral route	TSCA.
Chloroethane	24A	Dose-response data in animals for acute- and intermediate-duration oral exposures. The subchronic study should include an evaluation of immune and nervous system (and behavior, demeanor) tissues, and extended reproductive organ histopathology.	TSCA. (EPA will only address the immune system requirement of this Priority Data Need)

TABLE 3.—PRIORITY DATA NEEDS POTENTIALLY BEING ADDRESSED BY VOLUNTARY RESEARCH

Substance	ID	Priority data need	Firm
PCBs	7B	Biodegradation of PCBs in water	General Electric Company.
	7E	Epidemiological studies on the health effects of PCBs (Special emphasis endpoints include: immunotoxicity, gastrointestinal, toxicity, liver, kidney, thyroid, toxicity, reproductive/developmental, toxicity).	General Electric Company.
Methylene chloride	20A	Dose-response data in animals for acute- and intermediate-duration oral exposure. The subchronic study should include extended reproductive organ histopathology, neuropathology and demeanor, and immunopathology.	Halogenated Solvents Industry Alliance.
	20B	2-species developmental toxicity study via the oral route	Halogenated Solvents Industry Alliance.

TABLE 4.—PRIORITY DATA NEEDS BEING ADDRESSED BY MHPF INSTITUTIONS

Substance	ID	Priority data need	Institution
Lead	1A	Mechanistic studies on the neurotoxic effects of lead	Florida A & M University. Texas Southern University.
	1C	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	The King/Drew Medical Center of the Charles R. Drew University of Medicine and Science. Morehouse School of Medicine.
Mercury	3A	Multigeneration reproductive toxicity study via oral exposure.	Tuskegee University.
Benzene	5B	2-species developmental toxicity study via oral exposure.	Xavier University.
PAHs	9A	Dose-response data in animals for intermediate duration oral exposures. The subchronic study should include extended reproductive organ histopathology and immunopathology.	Meharry Medical College.
	9D	Dose-response data in animals for acute- and intermediate-duration inhalation exposures. The subchronic study should include extended reproductive organ histopathology and immunopathology.	Meharry Medical College.
Trichloroethylene	10B	Neurotoxicology battery of tests via oral exposure	Texas Southern University.

TABLE 4.—PRIORITY DATA NEEDS BEING ADDRESSED BY MHPF INSTITUTIONS—Continued

Substance	ID	Priority data need	Institution
Toluene	18C	Neurotoxicology battery of tests via oral exposure	Texas Southern University.
Zinc	21A	Dose-response data in animals for acute- and intermediate-duration oral exposures. The subchronic study should include an extended histopathological evaluation of the immunologic and neurological systems.	Xavier University. Tuskegee University.

TABLE 5.—PRIORITY DATA NEEDS BEING ADDRESSED BY THE ATSDR GREAT LAKES HUMAN HEALTH EFFECTS RESEARCH PROGRAM

Substance	ID	Priority data need	Institution
Lead	1C	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	State University of New York at Buffalo. State University of New York at Oswego. Michigan State University. University of Wisconsin—Superior. New York State Health Department. University of Illinois at Chicago. University of Illinois at Urbana-Champaign. Wisconsin Department of Health and Social Services.
Mercury	3A	Multigeneration reproductive toxicity study via oral exposure.	State University of New York at Oswego. University of Illinois at Chicago.
	3D	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	State University of New York at Buffalo. State University of New York at Oswego. Michigan State University. University of Wisconsin—Superior. New York State Health Department. University of Illinois at Chicago. University of Illinois at Urbana-Champaign. Wisconsin Department of Health and Social Services.
	3E	Potential candidate for subregistry of exposed persons.	Wisconsin Department of Health and Social Services.
PCBs	7A	Dose-response data in animals for acute- and intermediate-duration oral exposures.	University of Wisconsin—Superior.
	7E	Epidemiological studies on the health effects of PCBs (special emphasis endpoints include: immunotoxicity, gastrointestinal toxicity, liver, kidney, thyroid toxicity, reproductive/developmental toxicity).	State University of New York at Buffalo. State University of New York at Oswego. University of Wisconsin—Superior. University of Illinois at Chicago. University of Illinois at Urbana-Champaign.
	7F	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	State University of New York at Buffalo. State University of New York at Oswego. Michigan State University. University of Wisconsin—Superior. New York State Health Department. University of Illinois at Chicago. University of Illinois at Urbana-Champaign. Wisconsin Department of Health and Social Services.
PAHs	9E	Epidemiological studies on the health effects of PAHs (special emphasis endpoints include: cancer, dermal, hemolymphatic, and hepatic).	Wisconsin Department of Health and Social Services.
	9F	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	Wisconsin Department of Health and Social Services.
DDT	11D	Epidemiological studies on the health effects of DDT, DDD and DDE (special emphasis endpoints include: immunotoxicity, reproductive and developmental toxicity).	State University of New York at Buffalo. State University of New York at Oswego. Michigan State University. University of Illinois at Chicago. Wisconsin Department of Health and Social Services.
	11E	Exposure levels in humans living near hazardous waste sites and other populations, such as exposed workers.	State University of New York at Buffalo. State University of New York at Oswego. Michigan State University. University of Illinois at Chicago. Wisconsin Department of Health and Social Services.
	11F	Potential candidate for subregistry of exposed persons.	Wisconsin Department of Health and Social Services.

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