Chapter 4
Federal Attention to Immunotoxicants

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INTRODUCTION

A diverse framework of laws authorizes several Federal agencies to control human exposure to toxic substances, including immunotoxicants. This chapter describes Federal research activities designed to enhance the base of knowledge about immunotoxicology and to support regulatory efforts. This chapter also provides a brief summary of the power of the Federal regulatory agencies to license, register, set standards, or otherwise control immunotoxic substances. Several previous OTA studies have described Federal programs to regulate toxic substances in much greater detail (24,26,27,28,29,30,31,32). Finally, this chapter describes Federal programs that enable workers and the general public to obtain information about the presence of toxic substances as a means to control exposure.

FEDERAL RESEARCH ACTIVITIES

Federal immunotoxicology programs focus on research, development, and validation of test methods to assess the impact of substances on the immune system. Researchers seek improved methods for assessing the toxicological bases of hypersensitivity, autoimmunity, and immune suppression. This section discusses Federal efforts to evaluate substances that may present immunotoxic health risks and to develop immunotoxicological tests for use in regulation.

The National Toxicology Program

The Secretary of the U.S. Department of Health and Human Services(HHS) established the National Toxicology Program (NTP) in 1978 to coordinate and strengthen the Department's activities in characterizing the toxicity of chemicals. NTP is charged with:

- broadening the spectrum of toxicologic information obtained on selected chemicals;
- increasing the numbers of chemicals studied, within funding limits;
- developing and validating assays and protocols responsive to regulatory needs; and
- communicating NTP plans and results to governmental agencies, the medical and scientific communities, and the public.

NTP consists of four charter agencies of HHS: the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), the National Center for Toxicological Research (NCTR), and the National Institute for Occupational Safety and Health (NIOSH). NTP coordinates the relevant programs,staff, and resources from those Public Health Service agencies relating to basic and applied toxicological research, An executive committee consisting of the heads of the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), NIEHS, the Agency for Toxic Substances and Disease Registry (ATSDR), the Consumer Product Safety Commission (CPSC), NCI, NIOSH, and the Occupational Safety and Health Administration (OSHA) oversees NTP. Nominations of chemicals for toxicology studies are made by all participating agencies and are encouraged from all sectors of the public.

The objectives of NTP's immunotoxicology Program are to systematically: 1) evaluate and examine the influence of selected chemicals on the immune response; 2) relate alterations in immunologic functions to both general toxicity and specific organ toxicity; 3) relate changes in immunologic functions to altered host resistance; and 4) refine and employ a panel of immune and host resistance test procedures in order to better define in vitro and in vivo immunotoxicit y. The immunotoxicology Program seeks to correlate laboratory immunologic findings with altered host susceptibility and to extrapolate animal findings about chemically induced effects to estimates of human risk (17).

NTP researchers conceived a tier approach to testing for immunosuppression (12; see ch. 3). Tier I (see table 4-1) includes assays for pathology, humoral immunity,

Table 4-1—NTP's Panel of Tests for Detecting immunotoxicity

Parameter	Procedures
Screen (Tier 1)	
Immunopathology	Hematology-complete blood count and differential Weights-body, spleen, thymus, kidney, liver Cellularity—spleen Histology-spleen, thymus, lymph node
humoral-mediated immunity	Enumerate IgM antibody plaque forming cells to T-dependent antigen(SRBC) LPS mitogen response
Cell-mediated immunity	Lymphocyte blastogenesis to mitogens (Con A) and mixed leukocyte response against allogeneic leukocytes (MLR)
Nonspecific immunity . .	Natural killer (NK) cell activity
Comprehensive (Tier 11)	
Immunopathology	Quantitation of splenic B and T cell numbers
humoral-mediated immunity	Enumeration of IgG antibody response to SRBCs
Cell-mediated immunity	Cytotoxic T lymphocyte (CTL) cytolysis. Delayed hyper-sensitivity response (DHR)
Nonspecific immunity . .	Microphage function-quantitation of resident peritoneal cells, and phagocytic ability (basal and activated by MAF)
Host resistance challenge model (endpoints)	Syngeneic tumor cells PYB6 sarcoma (tumor incidence) B16F1O melanoma (lung burden) Bacterial models *Listeria monocytogenes* (mortality) *Streptococcus* species (mortality) Viral models Influenza (mortality) Parasite models *Plasmodium yoelii* (parasitemia)

SOURCE: Ml. Luster, A.E. Munson, P.T. Thomas, et al., "Methods Evaluation—Development of a Testing Battery to Assess Chemical-Induced immunotoxicity: National Toxicology Program's Guidelines for immunotoxicity Evaluation in Mice," *Fundamental and Applied Toxicology 10:2-19, 1988.*

cell-mediated immunity, and nonspecific immunity. The tests included in Tier I function as a basic immunotoxicity screening mechanism and cannot predict whether a substance will reduce the immune system's ability to fight disease. However, they can detect immune alterations that suggest the need to evaluate the compound further, using one or more of the specialized tests listed under Tier II. Tier II assays include pathologic tests and measures of humoral, cell-mediated, and nonspecific immunity, and employ host resistance challenge models that test the ability of an animal (usually a mouse) to prevent infection or tumor growth after exposure to a suspected immunotoxicant. NTP's battery of tests does not include measures of a substance's potential to induce hypersensitivity. NTP's methods cannot measure tolerance or reversibility of effect, since animals are evaluated at a single point in time, or specific sites of immune responsiveness, such as lung or intestinal immunity.

Since 1985, when validation of the NTP tiers was completed, more than 50 chemicals have been evaluated for immunosuppression (see table 4-2). NTP has also tested 2 of those chemicals and 15 additional chemicals using standard hypersensitivity assays (see table 4-3). Among the agents tested by NTP are the AIDS treatment, AZT; nitrophenylpentadien — spy dust; methyl isocyanate, the primary causative agent of the Bhopal disaster; and silicone fluid used in surgical implants.

The mouse has been the experimental animal of choice at NTP because its immune system is well characterized. Efforts are underway to validate immunotoxicity

Table 4-2—Substances Tested by NTP for Immunosuppression

Substance	Use/Industry	immunotoxicity
acetonitrile	catalyst; solvent	
aldicarb oxime	insecticide	
allyl isovalerate	fragrance; flavoring agent	–
arsine	dopant for microelectronics	+
azathioprine	chemotherapeutic agent	+
benzidine	drycleaning fluid; dye manufacturing	+
benzo (a) pyrene	fossil fuel combustion byproduct	+
benzo (e) pyrene	veterinary antiseptic	–
o-benzyl- p-chlorophenol	germicide	
t-butylhydroquinone	antioxidant in cosmetics	–
cadmium chloride	photography; dyes; lubricants	+
chemical mixture	mix of 26 groundwater contaminants	+
4-chloro-o-phenylenediamine	hair dyes; curing agent	
cyclophosphamide	cancer therapeutic	+
2,4-diaminotoluene	photography	+
dideoxyadenosine	potential AIDS therapeutic	+
diethylstilbestrol	formerly a hormone therapy; cattle growth promoter	+
dimethylbenz(a) anthracene	induces malignant tumors (research)	+
dimethyl vinylchloride	organic synthesis	+
diphenylhydantoin	anticonvulsant therapeutic	+
ethyl carbamate	anesthetic; co-solvent; anti-neoplastic	+
ethylene dibromide	fumigant; gasoline additive	+
formaldehyde	disinfectant; tissue fixative; textiles; photography; wood products	–
gallium arsenide	semiconductors; electronics; microwave generation	+
ginseng	medicinal and research purposes	+
hexachlorobenzo-p-dioxin	chemical byproduct	+
indomethacin	analgesic; anti-inflammatory	+
interferon-alpha	cell product with antiviral activity	+
lithium carbonate	glazes; antidepressant drug	+
methyl carbamate	chemical intermediate	–
methyl isocyanate	synthesis of pesticides	
nickel sulfate	fabrics; plating; catalyst	–
nitrobenzene	dyes; shoe polish; leather; paint; soaps	+
nitrofurazone	antibacterial agent; food additive	–
n-nitrosodimethylamine	solvent; rocket fuels; antioxidant	+
m-nitrotoluene	explosives; dyes	+
p-nitrotoluene	explosives; dyes	+
ochratoxin a	metabolize from mold	+
oxymetholone	therapeutic; synthetic androgen	–
pentachlorophenol	wood preservative	+
pentamidine isethionate	antiprotozoal used to treat pneumonia	
o-phenylphenol	fungicide; cleaning; rubber; preservative	–
phorbol myristate acetate	tumor promoter (research)	+
ribavirin	antiviral therapeutic	+
silicone polymers	semiconductor manufacture; surgical implants	–
2,3,7,8 -tetrachlorodibenzo-p-dioxin	herbicide production byproduct	+
tetraethyl lead	chemical intermediate	+
tetrahydrocannibinol	constituent of marijuana	–
4,4-thiobis(6-t-butyl-m-cresol)	antioxidant and stabilizer	+
toluene	solvent; denaturant	–
tris(2,3-dichloropropyl) phosphate	flame retardant	–
vanadium pentoxide	catalyst; glass; ceramics; photos; textiles	–
4-vinyl-1- -cyclohexene diepoxide	resins	+

NOTE: Positive (+) compounds demonstrated a significant dose-response effect for any one parameter in the NTP Tiers or showed significant effects in multiple parameters at a high dose level. The designation indicates potential immunosuppresive chemicals, not definitive immunotoxicants.

SOURCE: Office of Technology Assessment, 1991; based on Ml. Luster, National Institute of Environmental Health Sciences, Research Triangle Park, NC, personal communication, July 1990.

testing in rats because they are used most frequently in general toxicological testing. The goal of toxicological testing on experimental animals is to be able to extrapolate from test results to human health effects. Thus researchers may proceed with testing and test validation in other species (e.g., dogs, swine, and primates) in order to identify the most suitable test subjects for particular immune functions.

in fiscal year 1990, NTP had a budget of almost $2.6 million for immunotoxicological research (19). NTP continues to work on refining and improving the immu-

Table 4-3-Substances Tested by NTP for Hypersensitivity

Substance	Use/industry	immunotoxicity
benzothonium chloride	veterinary medicine	
benzyl-p-chlorophenol	disinfectant germicide	+
4-chloro-o-0-phenylenediamine	hair dyes; curing agent	+
cobaltous sulfate	electroplating; glazes	+
crotonaldehyde	solvent; warfare	–
2,4-diaminotoluene	photography	
dinitrofluorobenzene	reagant	+
ethylene thiourea	electroplating; dyes; rubber	+
glutaraldehyde	disinfectant; fixative	+
isobutyraldehyde	perfumes; rubber; antioxidants	
isophorone diisocyanate	polyurethane	+
2-mercaptobenzothiazole	rubber; fungicide; oil	+
nitrophenylpentadien	spy dust	
oleic acid diethanolamine	surfactant	
polydimethylsiloxane fluid	water repellant; resin; surgical implants	
triethanolamine	dry cleaning; cosmetics; textiles	
xylenesulfonic acid	shampoos;cleaning compounds	

NOTE: Positive (+) indicates statistically significant contact hypersensitivity response observed in mice and/or guinea pigs.

SOURCE: Office of Technology Assessment, 1991; based on Ml. Luster, National Institute of Environmental Health Sciences, Research Triangle Park, NC, personal communication, July 1990.

notoxicity test battery, and is currently engaged in reviewing data to determine whether the Tier I and Tier II assays can predict the immunotoxicity of compounds and the potential for use of the test data in risk assessment (34).

The Environmental Protection Agency

EPA's primary immunotoxicological research efforts are located in the Office of Health Research (OHR). In fiscal year 1990, OHR had 6 principle investigators engaged in immunotoxicological research and funded $345,000 of intramural research and $324,000 of extramural research (22).

EPA's research program in immunotoxicology has four primary goals:

- to develop tier testing methods in the rat similar to those used by NTP in the mouse. This effort, which is coordinated with NTP, supports guideline development for the Office of Pesticide Programs and the Office of Toxic Substances;
- to develop host resistance assays for both the mouse and rat that can be included in test guidelines, which would facilitate use of immunotoxicity testing data for risk assessment purposes;
- to develop methods for assessing immune responses in the lung (including development of appropriate host resistance models) in order to improve the ability to assess immunotoxic effects of inhaled compounds. These methods are used to evaluate National Ambient Air Quality Standard (NAAQS) pollutants as well as other compounds covered by the Clean Air Act. Such methods are needed because of the diffuse nature of the immune system and because many of the inhaled compounds assessed primarily affect the lung rather than the spleen from which cells are usually obtained for immune function tests. Effects of certain air pollutants on markers of immune dysfunction in the lung are also being assessed in human clinical studies; and
- to develop improved methods for assessing allergenic potential of compounds, including methods development in both contact sensitivity and pulmonary hypersensitivity (22).

In addition to work in the immunotoxicology program of OHR, EPA scientists have established an oral reference dose for tributyltin oxide (an antimicrobial/antifungal pesticide) based on immunotoxic concerns. The reference dose may eventually be used by regulatory offices within the agency to set exposure standards.

The Food and Drug Administration

FDA has contributed substantially to the field of immunotoxicology and held one of the first scientific conferences on inadvertent modification of immune response. Four centers of the FDA, the Center for Food

Safety and Applied Nutrition (CFSAN), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER), and NCTR are currently engaged in basic immunotoxicity research and test development.

FDA uses different immunotoxic testing strategies depending on the substance tested and its intended uses, thus a standardized testing scheme is unsuited to FDA's needs. CFSAN has been involved in immunotoxicological research since the mid-1970s, when it began to develop in vitro studies to screen for potentially immunotoxic food constituents and contaminants. Current research efforts involve methods development as well as actual studies of the immunotoxic potential of food additives and contaminants. CFSAN is trying to integrate immunotoxicity with conventional toxicity testing and may soon issue guidelines for evaluating the immunotoxic potential of direct food additives (11).

immunotoxicology research efforts at CBER are aimed at better understanding the clinical relevance of compromised immune function (5). CDER evaluates drugs on a case-by-case basis and encourages immunotoxicity testing by manufacturers where it is warranted (14). The NCTR initiated an immunotoxicity research program in 1975, and the major focus of NCTR'S research program has been on development of in vivo testing (2). FDA states that much of its workload is directly related to identifying possible toxic effects on the immune system, and the agency was unable to respond to OTA's inquiry about budget and personnel devoted specifically to immunotoxicology (3).

Other Federal Research Efforts

The NIH allocated approximately $27 million to immunotoxicological research in fiscal year 1989 (some of which went to NTP) (16). Funds for intramural and extramural research have been available at varying levels in each of the Institutes. Much of the immunotoxicity research was incidental to other research efforts, but immunotoxicology received some direct attention. For instance, the National Institute of Allergy and Infectious Diseases has supported dermatotoxicological studies of allergenic plants, assessment of how chemical additives in foods and medications can trigger asthmatic attacks, and animal studies on the causal role of workplace chemicals in asthma.

NIEHS spent approximately $7.5 million on immunotoxicological research in fiscal year 1989. NIEHS is actively involved in developing and validating immunotoxicological test methods, and provides funding for NTP's immunotoxicity testing program. NIEHS, working independently and through NTP, also performs basic research, seeking to better define the relationship between immune function changes and altered host resistance, particularly at the low end of the dose-response curve, as well as provide data that should support a framework to allow better extrapolation from animal immunotoxicity data to human health risks.

The Centers for Disease Control (CDC) also conduct immunotoxicity research. The Center for Environmental Health and Injury Control allocated $175,000 and two full-time equivalent staffers (FTEs) to a study of immunology measurements for human exposure assessment in fiscal year 1990. NIOSH conducted an assessment of immunological markers of herbicide exposure in fiscal year 1990, and provided basic support to immunotoxicological research for a total budget of over $300,000 and four FTEs. The Agency for Toxic Substances and Disease Registry (ATSDR) also provides financial support to much of CDC'S immunotoxicology research (8).

The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) carries out research to determine the effects of alcohol and abused drugs on the immune system. ADAMHA has a particular interest in the interaction between the nervous system and the immune system (6). The Department of Defense reported that it funded, in fiscal year 1990, one extramural immunotoxicity research project designed to develop a model for studying the toxicity of dioxin (15). The Department of Agriculture reported that it does not single out immunotoxic substances for research, but indicated significant research attention to aflatoxin, which has shown evidence of immunotoxicity (21).

Because of significant differences in data collection and reporting among the agencies, OTA could not arrive at an exact budget for federally supported immunotoxicological research for this background paper. Most of the agencies charged with protecting human health have some ongoing immunotoxicological research activities, much of it devoted to developing and validating tests that can be applied to substances of concern to the

agencies. There is strong interest among the Federal agencies–particularly FDA, NIH, CDC, and EPA– to organize a Federal interagency committee on immunotoxicology to foster increased interaction among the agencies responsible for immunotoxicity research programs (4).

FEDERAL REGULATORY ACTIVITIES

OTA identified 12 laws with mandates broad enough to encompass immunotoxicological concerns that authorize Federal agencies to regulate toxic substances (table 4-4). None of these laws spells out a specific duty to regulate immunotoxicants, but the duty to protect human health included in each law places immunotoxicants within the regulatory reach of the administering agencies.

The Occupational Safety and Health Administration

OSHA administers the Occupational Safety and Health Act (OSH Act) of 1970 (29 U.S.C. 651 et seq.). The Act authorizes OSHA to promulgate new standards for toxic materials and to modify or revoke existing standards. Section 655(b)(5) states that:

> The Secretary, in promulgating standards dealing with toxic materials or harmful physical agents under this subsection shall set the standard which most adequately assures, to the extent feasible on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life.

The Supreme Court has interpreted this language to require OSHA to enact the most protective standard possible to eliminate a significant risk of material impairment, subject to the constraints of technological and economic feasibility *(American Textile Manufacturers Institute, Inc. v. Donovan, 452* U.S. **490 (1981)).**

OSHA rulemaking can result in requirements for monitoring and medical surveillance, workplace procedures and practices, personal protective equipment, engineering controls, training, recordkeeping, and new or modified permissible exposure limits (PELs). In 1987, OSHA adopted updated standards that had been set by the American Conference of Government Industrial Hygienists (ACGIH), a voluntary organization, for workplace exposure to 428 toxic substances (52 FR 2332; 29 CFR Part 1910). Despite these new standards, OSHA lacks information on the effects of chronic exposure for over 90 percent of these substances. Most of the remaining 10 percent, which have been evaluated for chronic toxicity, have not been evaluated for immunotoxicity (36). However, an immunotoxic effect, sensitization, was specifically noted for eight of these substances (table 4-5).

Table 4-4—Major Federal Laws Controlling Toxic Substances

Act	Agency primarily responsible
Toxic Substances Control Act.	EPA
Federal Insecticide, Fungicide, and Rodenticide Act	EPA
Federal Food, Drug, and Cosmetic Act	FDA
Occupational Safety and Health Act.	OSHA
Comprehensive Environmental Response, Compensation, and Liability Act.	EPA
Clean Air Act	EPA
Federal Water Pollution Control Act and Clean Water Act..	EPA
Safe Drinking Water Act	EPA
Resource Conservation and Recovery Act..	EPA
Consumer Product Safety Act	CPSC
Federal Hazardous Substances Act.	CPSC
Federal Mine Safety and Health Act	MSHA

KEY: CPSC-Consumer Product Safety Commission; EPA—Environmental Protection Agency; FDA—Food and Drug Administration; MSHA—Mine Safety and Health Administration; OSHA--Occupational Safety and Health Administration

SOURCE: Office of Technology Assessment, 1991.

Photo credit: Environmental Protection Agency, Washington, DC

Special clothing, as well as exposure limits, can help protect workers.

Table 4-5-Sensitizers Regulated by OSHA

Substance	Use/industry	Health effects
Captafol	fungicide	Skin and respiratory sensitization
Cobalt (metal, dust, and fume)	aircraft; automobile	Pulmonary sensitization
Isophorone diisocyanate	housing; automobile	Skin and respiratory sensitization
Phenothiazine	veterinary insecticide	Skin sensitization
Phenyl glycidyl ether	monomer and surfactant production	Skin sensitization
Picric acid	rocket fuels; steel	Skin sensitization
Subtilisins	laundry detergents	Respiratory sensitization
Toluene-2,4-diisocyanate	rubber; paints; coal tar	Pulmonary sensitization

SOURCE: Federal Register, vol. 53, No. 109, Tuesday, June 7, 1988.

The Food and Drug Administration

FDA regulates chemicals found in foods, drugs, and cosmetics under the Food, Drug, and Cosmetic Act of 1938 (FDCA; 21 U.S.C. 301-392). FDCA encompasses several laws passed by Congress since the first Federal statute regulating food safety, the Food and Drugs Act of 1906, including the Pesticide Chemical Residues Amendment of 1954, the Food Additives Amendment of 1958, the Color Additive Amendments of 1960, the Drug Amendments of 1962, and the Animal Drug Amendments of 1%8.

Foods

FDCA declares it illegal to sell an adulterated food. A food is adulterated if:

> . . . it bears or contains any poisonous or deleterious substance which may render it **injurious to** health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health (21 U.S.C. 342(a)).

FDA has authority to regulate unavoidable environmental contaminants, pesticide residues, and additives that appear in food. Added substances are governed by a stricter standard than naturally occurring substances. FDA has authority to require premarket submission of specific toxicity test data. FDA does not currently have testing guidelines for immunotoxicity in foods, but CFSAN has proposed some guidelines that are currently under review (11).

FDA regulates some substances studied as immunotoxicants, such as mercury and polychlorinated biphenyls (PCBs), based upon other adverse health effects (21 CFR Part 189). FDA regulated Yellow Dye No. 5 based on its association with hypersensitivity. FDA has also regulated the use of sulfites because they can provoke life-threatening responses– often severe asthmatic attacks— in sensitive individuals. Sulfites are no longer generally recognized as safe for use on fruits or vegetables intended to be served or sold raw or presented as fresh to consumers, or on potatoes intended to be served or sold unpackaged and unlabeled to consumers (21 CFR Part 182).

Drugs

FDCA authorizes FDA to regulate new drugs for humans and animals. The Public Health Service Act provides similar authority for biologics (e.g., vaccines, monoclinal antibodies, cytokines, and growth factors). New drugs and biologics require pre-marketing approval. In the approval process, applicants must submit two kinds of applications: 1) an Investigative New Drug (IND) application, essentially a request to conduct an investigation; and 2) a New Drug Application (NDA) or Product Licensing Application (PLA), essentially a request for permission to conduct a more detailed investigation adequate to achieve marketing approval.

The IND application must include chemical, manufacturing, and control information; pharmacologic and toxicologic information from animals and in vitro systems; and a plan of clinical study. An NDA or PLA, submitted after the research period for the IND, must include full reports of toxicological studies and clinical investigations to show that the test agent is safe and effective; a complete list of the test agent's composition; samples of the test agent; information that may be re-

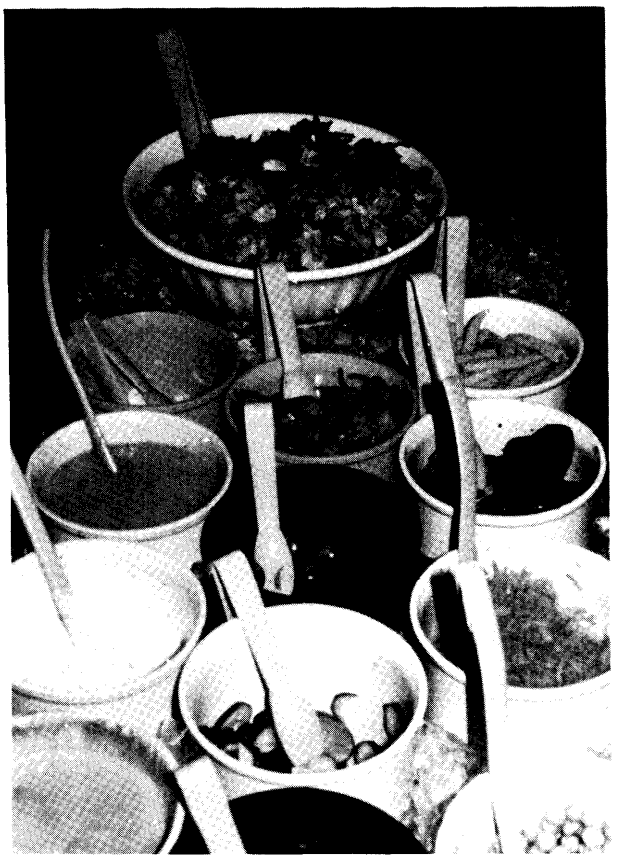

Photo credit: Julios, Washington, DC-- Onrubia

Federal regulations now prohibit the use of sulfites on salad bars because they evoke hypersensitivity reactions.

quired for monitoring; specimens of proposed labels; and information on the potential risks of inactive ingredients.

The mechanisms of immunosuppression and its clinical consequences are better understood than those of immunostimulation, due largely to experience with immunosuppressive drugs in clinical practice. FDA has approved the use of several drugs as immunosuppressive agents, such as cyclosporin A. In addition, FDA has approved drugs whose known immunotoxic effects, particularly sensitization, are outweighed by their benefits, but generally requires a warning of sensitization as a possible side effect. In CDER, each division routinely evaluates immunotoxicity as part of the total safety assessment. Many of the tests for effects on the immune system are routinely incorporated into the 28-day toxicity studies that are usually submitted as part of the IND (14). FDA's drug testing guidelines do not specifically require immunotoxicity testing, but require that an applicant convince FDA that its test data are adequate. FDA can suggest or require immunotoxicity testing where appropriate.

Cosmetics

FDA cannot, under the law, require a manufacturer to perform toxicity testing of cosmetic ingredients, However, products that have not been tested for safety cannot be marketed unless they bear a label reading *"Warning. The safety of this product has not been determined" (21 CFR 740.10).*

FDA has restricted fewer than 20 cosmetic ingredients on the finding that they were "poisonous or deleterious." Among these restricted ingredients, however, are substances known to affect the immune system, such as mercury and mercurial compounds, potent allergens and contact sensitizers (21 CFR 700.13), and vinyl chloride, a contact sensitizer (21 CFR 700.14). Despite FDA's inability to compel toxicity testing, the cosmetic and fragrance industries do operate voluntary testing programs for potential skin sensitizers (7).

The Environmental Protection Agency

EPA administers several laws that authorize regulation of toxic substances, including the Clean Air Act (CAA; 42 U.S.C. y 7401 et seq.), the Clean Water Act (CWA; 33 U.S.C. 1251 et seq.), the Safe Drinking Water Act (SDWA; 42 U.S.C. 201, 300f et seq.), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA; 7 U.S.C. 136 et seq.), the Toxic Substances Control Act (TSCA; 15 U.S.C. 2601 et seq.), the Resource Conservation and Recovery Act (RCRA; 42 U.S.C. 6901 et seq.), and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA; 42 U.S.C. 9601 et seq.).

The Clean Air Act

Under the CAA, EPA regulates air pollutants by setting National Primary and Secondary Ambient Air Quality Standards as necessary to protect the public

health and welfare. EPA has promulgated primary National Ambient Air Quality Standards for sulfur oxides, particulate matter, carbon monoxide, ozone, nitrogen dioxide, and lead (40 CFR 50). None of these standards was based on consideration of immunotoxic effects, although ozone, nitrogen dioxide, and lead have all shown evidence of immunotoxicity in animal tests.

The 1970 amendments to the CAA also called for EPA to set standards limiting hazardous pollutants. Section 112 of the CAA authorizes EPA to set emissions standards for pollutants that may reasonably be anticipated to result in an increase in mortality or an increase in serious, irreversible, or incapacitating reversible illness. The list of substances designated by EPA as hazardous air pollutants includes asbestos, benzene, beryllium, coke oven emissions, inorganic arsenic, mercury, radionuclides, and vinyl chloride (40 CFR Part **61).** Several of time substances have shown evidence of immunotoxicity in the laboratory, but serious health effects other than immunotoxicity served as the basis for these standards, which set exposure levels far below those used in the tests.

Amendments to the CAA passed by the 10lst Congress (Public Law 101-549) establish a statutory list of 189 hazardous substances or classes of substances. The EPA Administrator may add or delete substances based on evidence of a pollutant's potential to cause in humans:

(i) cancer or developmental effects, or
(ii) serious or irreversible–

Photo credit: Environmental Protection Agency, Washington, DC

Few data exist on the human health risks from transient, low-level chemical exposures.

(I) reproductive dysfunctions,
(II) neurological disorders,
(III) heritable gene mutations,
(IV) other chronic health effects, or
(V) adverse acute human health effects.

The 1990 amendments direct EPA to require application of the maximum achievable control technology (MACT) initially. Following implementation of MACT, EPA is required to evaluate residual risk from sources of these substances and decide whether public health is adequately protected; if not, stricter controls can be required.

The Clean Water Act

Since the Federal Water Pollution Control Act was first enacted in 1948, it has been amended nine times and is now generally referred to as the CWA. The 1972 amendments set the goal of achieving "fishable, swimmable" waters by 1983 and prohibiting the "discharge of toxic pollutants in toxic amounts" by 1985. The 1977 amendments endorsed anew method for regulating toxic pollutants, and the 1987 amendments continued Congress's emphasis on control of toxic pollutants.

The CWA authorizes the EPA administrator to establish and revise a list of toxic water pollutants. EPA may then issue effluent limitations or effluent standards to regulate discharges of these substances into the Nation's navigable waters. Effluent limitations, established on an industry-by-industry basis, impose technology-based restrictions on the amount of a toxic substance that can be directly discharged from a point source. Effluent standards are control requirements based on the relationship between the discharge of a pollutant and the resulting water quality in a receiving body of water. Effluent standards can be imposed when, in the judgment of the Administrator, the effluent limitations affecting a particular source are insufficient to protect the designated use of a particular water body reflected in the water quality standard for that body established by the State. This more stringent effluent *standard is* employed much less frequently than the technology-based effluent limitations.

The CWA also requires that EPA establish pretreatment standards for toxic substances discharged from private pollution sources into publicly owned water treatment facilities. In addition to these legally binding regulations, the CWA authorizes EPA to establish ambient

water quality criteria for all pollutants, including toxics, to be used as water quality goals.

EPA has published **a list** of hazardous substances under the CWA (40 CFR 116.4) and has established reportable quantities for each of these substances (40 CFR 117.3). Under the CWA, EPA has also promulgated toxic pollutant effluent standards for six substances (40 CFR Part 129), including PCBs (known to be immunotoxic in laboratory animals). immunotoxicity was not the endpoint of concern in these rulemaking procedures, however.

The Safe Drinking Water Act

The SDWA regulates public **waters** systems and addresses contaminants "which may have an adverse effect on the health of persons." Under the SDWA, EPA establishes maximum contaminant levels goals for contaminants that may have an adverse effect on health. These are nonenforceable health goals, which are used as guidelines for establishing enforceable drinking water standards. EPA then sets enforceable "maximum contaminant levels" (MCL) that are as close to the goal as feasible considering the best available technology and the economic costs of complying with the standard. MCLs have been set for inorganic chemicals (40 CFR 141.11 and 141.62) organic chemicals (40 CFR 141.12 and 141.61). Immunotoxicity was not a noted consideration in these actions.

The Federal Insecticide, Fungicide, and Rodenticide **Act**

FIFRA makes it unlawful to sell or distribute a pesticide that is not registered with EPA. An applicant for registration of a pesticide must file the following information with EPA: a statement of all claims made for the pesticide; directions for its use; a description of tests made upon it; and the test results used to support claims made for the substance. In addition, the applicant must supply appropriate health and safety data. EPA must register the pesticide if its composition warrants the proposed claims for it, if it will perform its intended function without unreasonable adverse effects on the environment, and if, when used in accordance with widespread and commonly recognized practice, it will not generally cause unreasonable adverse effects on the environment. An "unreasonable adverse effect on the environment" is defined as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." The burden of proof regarding safety is on the manufacturer. If EPA finds that a pesticide meets or exceeds any of its specified criteria for risk (40 CFR **154.7), it** must initiate a special review process. This process allows EPA to require additional toxicity testing including immunotoxicity, if warranted.

A pesticide may be registered for general or restricted use, and EPA may conditionally register pesticides even if some test data are unavailable. EPA has concentrated its attention to date on the active ingredients in pesticides, but expresses increasing concern about inert ingredients. EPA has issued no restrictions on pesticide use based solely on immunotoxicity. The 1988 amendments to FIFRA require EPA to review 600 active ingredients of existing pesticides by 1997, which requires reexamination of safety, including toxicity. The test guidelines for reregistration are the same as for registration.

In 1982, EPA's Office of Pesticide Programs (OPP), which administers FIFRA, published data requirements for the toxicological evaluation of biochemical pesticides and for microbial pesticides. Biochemical pesticides include pheromones, hormones, natural insect and plant growth regulators, and enzymes. Microbial pesticides include bacteria, fungi, protozoa, and viruses. OPP recently revised the requirements to reflect advances in toxicology (23). The immunotoxicity study now required for biochemical pesticides is designed to accommodate either the rat or the mouse as the test animal. The tiered testing scheme as revised is presented in table 4-6. The study is required for biochemical pesticides where uses result in significant human exposure (e.g., food uses, indoor aerosols). Tier I tests serve as a screen for immunotoxic potential, and Tier II tests are designed to provide information necessary to perform risk assessment. Tests to determine whether biochemical pesticides can induce a delayed-type hypersensitivity reaction in guinea pigs are required and are set forth as a separate study in the data requirements (40 CFR 158.690).

The revisions of the data requirements deleted the requirement for specific immunotoxicity testing of microbial pesticides, but the ability of the test animals to clear the active microbial ingredient after dosing via oral, pulmonary, and intravenous routes is used as an indicator of a properly functioning immune system. EPA reserves the right to require an immunotoxicity study for certain microbial pesticides, but this study would be reserved for certain viruses that are related to viruses known to impact adversely on the human immune system (23). The requirement for a hypersensitivity assessment of

Table 4-6-EPA Subdivision M Guidelines: Proposed Revised Requirements for immunotoxicity Testing of Biochemical Pest Control Agents

Tier /
A. Spleen, thymus, and bone marrow cellularity
B. humoral immunity-do one of the following:
1. Primary and secondary immunoglogulin (lgG and lgM) responses to antigen
2. Antibody plaque forming cell assay
C. Specific cell-mediated immunity—do one of the following:
1. One-way mixed lymphocyte reaction (MLR) assay
2. Effect of BPCA on normal delayed-type hypersensitivity
3. Effect of BPCA on generation of cytotoxic T-lymphocyte
D. Nonspecific cell-mediated immunity:
1. Natural killer cell activity
2. Microphage function
Tier II
A. Tier II studies required if:
1. Dysfunction is observed in Tier I tests
2. Tier I test results cannot be definitively interpreted
3. Data from other sources indicate immunotoxicity
B, General testing features:
1. Evaluate time-course for recovery from immunotoxic effects
2. Determine whether observed effects may impair host resistance to infectious agents or to tumor cell challenge
3. Perform additional specific, but appropriate, testing essential for evaluation of potential risks

SOURCE: Office of Technology Assessment, 1991.

microbial pesticides also has been dropped, with reporting of any observations of allergic reactions being required instead. This is because it is expected that proteinaceous components of microbial pesticide preparations (including fermentation byproduct ingredients) would elicit a positive response in test guinea pigs after subcutaneous induction and challenge; and would most likely not give a positive response with topical induction and challenge.

OPP plans to revise its testing guidelines for chemical pesticides to include immunotoxicity testing Laboratory studies presently required for registration of chemical pesticides include a battery of acute toxicity studies (oral, dermal, pulmonary, eye), subchronic studies, chronic studies, developmental toxicity studies, reproduction effects study, battery of mutagenicity studies, chronic carcinogenicity study, and metabolism study (23).

The Toxic Substances Control Act

TSCA authorizes EPA to regulate chemicals (specifically excluding pesticides; tobacco and tobacco products; nuclear materials; foods, drugs, and cosmetics; pistols, firearms, revolvers, shells, and cartridges, which are regulated under other statutes) before and after they reach the market. EPA's first task under TSCA was to compile an inventory of all existing chemical substances that would be subject to the provisions of TSCA that were manufactured or imported into the United States in 1977. Any chemical not on that initial list is a "new" chemical and subject to premanufacture notice (PMN) requirements.

TSCA requires manufacturers to notify EPA in advance of the intended introduction into commerce of a new chemical with a Premanufacture Notice (PMN). EPA must also be notified if a chemical is to be used in away that differs significantly from that proposed in the original PMN. The PMN contains data on a chemical's identity and structure, proposed use, manufacturing byproducts, and impurities.

TSCA does not require that manufacturers carry out a specific program of toxicity testing before approval of a new chemical, thus PMNs are rarely submitted with toxicity data for each organ system. The extent of toxicity data submitted with PMNs generally depends on the projected annual production volume for the compound. If insufficient or incomplete toxicity data are provided to support a PMN, EPA requests additional information or issues a consent order in which the manufacturer agrees to provide the required information according to an established timetable.

EPA toxicologists evaluate PMNs by comparing new chemicals to structurally related existing chemicals. If toxicity is predicted on the basis of structural analogues, a chemical maybe subjected to a more detailed examination. If during the detailed review EPA concludes that a new chemical may present an unreasonable risk of adverse effects on human health or the environment, additional toxicity data can be required. Immunotoxicity has not been used as the basis for any regulatory action taken by EPA under the PMN provisions of TSCA.

TSCA also directs EPA to regulate existing chemical substances that pose an unreasonable risk of injury to human health or the environment and to act promptly on substances that pose imminent hazards. An Interagency Testing Committee reviews substances on the existing chemicals list and can recommend that EPA require

testing for these substances. In determining whether a chemical presents or may present an unreasonable risk to human health or the environment, EPA considers:

- the effects of a substance or mixture on human health and the magnitude of the exposure of human beings to it;
- the effects of a substance or mixture on the environment and the magnitude of the exposure of the environment to such substance or mixture;
- the benefits of such substance or mixture for various uses and the availability of substitutes for such uses; and
- the reasonably ascertainable economic consequences of the rules, after consideration of the effect on the national economy, small business, technological innovation, the environment, and public health.

If EPA can show that there is inadequate information on the effects of a chemical and that testing is necessary to obtain that information, it may issue a test rule defining the substances to be tested and how they should be tested. EPA has developed general guidelines for toxicity testing (40 CFR 796), but each test rule contains requirements specific to the chemical under scrutiny. Chemical manufacturers and processors are responsible for developing these test data, but EPA bears the burden of proof in establishing that a substance is an unreasonable risk to human health or the environment.

For either new or existing chemicals, EPA regulatory efforts may include steps to: prohibit their manufacture, processing, or distribution in commerce; limit their uses or amounts; require certain labeling; require maintenance of records and monitoring; prohibit or regulate any manner or method of commercial use; prohibit or regulate their disposal. Manufacturers or processors are required to notify EPA of any unreasonable risks posed by new or existing chemicals. immunotoxicity has been a noted concern in evaluations of chemicals under TSCA, but has not served as the health effect of primary concern in any regulatory action.

The Resource Conservation and Recovery Act

RCRA defines solid and hazardous wastes, authorizes EPA to set standards for facilities that generate or manage hazardous waste, and mandates a permit program for hazardous waste treatment, storage, and disposal facilities. Hazardous waste is defined as any solid waste that may cause death or serious disease, or may present a substantial hazard to human health or the environment if it is improperly treated, stored, transported, or disposed of. Lists of wastes subject to RCRA regulation can be found at 40 CFR 261.31, .32, and .33. The list contains known immunotoxicants, but immunotoxicity has not been the basis for any chemical's appearance on this list.

The Comprehensive Environmental Response, Compensation, and Liability Act

CERCLA (sometimes referred to as Superfund) requires anyone who releases significant amounts of hazardous substances into the environment to notify EPA. CERCLA defines hazardous substances as substances identified as toxic by the CWA, RCRA, CAA, or TSCA, and any substance which "when released into the environment may present substantial danger to the public health or welfare or the environment." CERCLA also requires that hazardous waste sites be cleaned up to a standard that ensures the protection of human health and environment. Reportable quantities (RQ) were set for each hazardous substance on the basis of aquatic toxicity, mammalian toxicity, ignitability, reactivity, chronic toxicity, and potential carcinogenicity. Immunotoxicity has been a consideration but not a primary factor in setting RQ standards.

Other Federal Regulatory Activity

EPA, FDA, and OSHA exercise the main regulatory authority over toxic substances, including immunotoxicants. Other agencies also administer laws that could be used to control these substances, however. The Consumer Product Safety Commission (CPSC), for instance, enforces the Consumer Product Safety Act (CPSA) (15 U.S.C. 2051 et seq.) and the Federal Hazardous Substances Act (FHSA) (15 U.S.C. 1261 et seq.).

The CPSA authorizes regulation of consumer products (except for foods, drugs, and cosmetics; pesticides; tobacco and tobacco products; motor vehicles; aircraft and aircraft equipment; and boats and boat accessories) that pose an "unreasonable risk" of injury or illness. CPSC may set safety standards that specify requirements for product performance or design, requirements for consumer instructions or warnings, or both. A

product c-an be banned if adequate safety standards are not feasible. No products have been regulated under CPSA on the basis of immunotoxicity.

The FHSA covers hazardous substances (excluding pesticides, foods, drugs, cosmetics, certain radioactive materials, and tobacco and tobacco products) in general use in the home, and is meant particularly to protect children from hazardous toys and products. A hazardous substance is a substance or mixture that may cause substantial personal injury or substantial illness as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children. A product can be required to bear a hazard label or it can be banned if labeling is inadequate to protect health. No products have been regulated under FHSA on the basis of immunotoxicity.

The Mine Safety and Health Administration (MSHA) regulates the exposure of miners to toxic substances under the Federal Mine Safety and Health Act Amendments of 1977 (30 U.S.C. 801 et seq.). Much of MSHA's regulation of toxic exposures involves incorporating by reference the lists of ACGIH. Some observers question use of the standards set by ACGIH since they historically have been set without reference to adequate research (36). On the other hand, as demonstrated by the very few standards that have been enacted by OSHA, hardly any workplace chemical exposures would be regulated if the ACGIH standards were not adopted by MSHA and OSHA (28).

FEDERAL INFORMATION PROGRAMS

Some Federal programs incorporate the assumption that an informed public is one means to decrease toxic exposures. Worker Right-to-Know programs, established by OSHA's hazard communication standard, and Community Right-to-Know programs, established by the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA), require that workers and other citizens be provided with knowledge about the toxic substances in their work or local environment. The Federal Government funds a national database at the National Library of Medicine that helps distribute information collected under EPCRA nationwide. Federal law also established the Agency for Toxic Substances and Disease Registry (ATSDR), which maintains a nationally available list of toxic substances and their health effects. The following section briefly describes each of these programs.

Worker Right-to-Know

In 1983, OSHA first established its hazard communication standard (29 CFR 1910.1200). This standard requires each employer to have a written hazard communication program for each workplace, including a list of all hazardous chemicals in the workplace. The employer is permitted to rely substantially on manufacturers and importers of chemicals to prepare the necessary information.

There are four basic elements of a hazard communication program. First, each manufacturer or importer of a chemical must determine whether that chemical is hazardous. A health hazard is defined as a chemical for which there is "statistically significant evidence based on at least one study conducted in accordance with scientific principles that acute or chronic health effects may occur." Second, each manufacturer or importer must prepare a material safety data sheet (MSDS) containing comprehensive information on the chemical, including all its hazards, precautions for safe handling and use, and control measures. These MSDS must be available to employees and customers. Third, employers must label containers to alert workers to the identity and significant hazards of the chemical. Finally, each employer must provide its workers with education and training in the handling of hazardous chemicals (13,20).

The standard requires disclosure of immunotoxic effects, where known. The standard does not permit OSHA to compel testing to determine unknown health effects, however. It should be noted that many MSDS contain very limited information on known toxic hazards (32), and those hazards that are described may be expressed in terminology unintelligible to the lay public (10).

Community Right-to-Know

Congress enacted EPCRA (42 U.S.C. 110001-11050) in response to releases of chemicals at Bhopal, India. EPCRA requires EPA to establish and maintain a list of "extremely hazardous substances." The current list includes 420 substances set out in 40 CFR Part 355 Appen-

dix A. EPA has developed a threshold planning quantity (TPQ) for each substance on the list.

This law requires owners and operators of facilities that store, use, or release extremely hazardous substances in amounts in excess of the TPQ to report to EPA information about those chemicals, their amounts, and their locations. EPCRA requires facility owners and operators to report releases of these chemicals into the environment whether from accidental spills or normal operations. The statute does not limit use or release of a substance; it merely requires that the public be informed (9).

Local community organizations must be notified of any offsite spills or any releases of a "reportable quantity" (RQ) of an extremely hazardous substance or a hazardous substance as defined in CERCLA. The RQ's for extremely hazardous substances are set out in 40 CFR Part 355, Appendix A. The list of hazardous substances and their RQ's under CERCLA are set out at 40 CFR 302.4. This emergency notification must include the chemical's common name, the lists on which it appears, the quantity released, the time and duration of the release, the media into which the release occurred, any acute or chronic health risks presented by the release, precautions to be taken, and the persons to contact for further information **(l).**

EPCRA community right-to-know provisions also require the public availability of material safety data sheets similar to those prepared under OSHA's hazard communication standard. The MSDS must contain the chemical and common names of the chemical, the chemical's physical and chemical characteristics, its physical and health hazards, its routes of exposure, precautions and emergency response procedures, exposure limits, and possible carcinogenic effects. If immunotoxic effects are among the known health hazards, they must be listed (35). Some research indicates that the MSDS, which were developed to convey information about workplace exposures, are unsuited to a community information program and that better means to communicate information about risk to the general public are needed **(10).**

National Library of Medicine: Toxicology Information Program

The National Library of Medicine (NLM) is the Nation's principal resource for the collection, organization, and retrieval of scientific literature in the health and biomedical fields (25). It has provided data about toxic chemicals and their hazards to the public for over 20 years. To enhance the accessibility of this information, NLM established the Toxicology Data Network (TOXNET). This database contains several files, including the Toxic Chemicals Release Inventory (TRI), which contains data on the estimated releases of toxic chemicals to the air, water, or land, as well as amounts transferred to waste sites. Current law requires U.S. industrial facilities to report the TRI information to EPA, which in turn provides it to NLM for public access. Searches of this file can be performed by region, company, chemical, but the file does not contain information on the health effects of, or human exposure to, these chemicals.

Another TOXNET file, the Hazardous Substances Data Bank (HSDB), covers chemical toxicity, as well as emergency handling procedures, environmental fate, human exposure, detection methods, and regulatory requirements. This file contains information on 4,200 chemicals. Most of the data in this file is taken from peer-reviewed journals. TOXNET also includes the Registry of Toxic Effects of Chemical Substances (RTECS), which covers 100,000 chemicals, and contains information on their acute and chronic effects, carcinogenicity, mutagenicity, and reproductive consequences. This file is not peer reviewed.

NLM also maintains the TOXLINE group of databases, outside TOXNET, which contains references to journal articles dealing with hazardous chemicals and other areas of toxicology and environmental health. At present, interested parties must contact a health science library or information center to request a TOXLINE

search. In the future, more public libraries may tie in to NLM. Individuals can request an application form to use NLM's system on a personal computer (33,18).

The Agency for Toxic Substances and Disease Registry

Congress created ATSDR in 1980, and its mission is to prevent or mitigate adverse human health effects and diminished quality of life resulting from exposure to hazardous substances in the environment. As part of its mission, ATSDR prepares toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health.

Each toxicological profile must include:

- an examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance;
- a determination of whether adequate information on the health effects of each substance is available or in the process of development; and
- an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

ATSDR also has a Division of Health Education which coordinates health communication and education activities for the Agency; coordinates development and educational activities for emergency response personnel; develops and disseminates to physicians and the health care providers materials on the health effects of toxic substances; establishes and maintains a list of areas closed or restricted to the public because of contamination with toxic substances; and initiates research. In addition, ATSDR has regional staff, located throughout the United States, who offer consultation on environmental health issues, including emergency response.

SUMMARY AND CONCLUSIONS

The Federal Government is actively involved in advancing the state-of-the-art of immunotoxicology. EPA, FDA, and NIH have immunotoxicological research programs, and each of these agencies contributes to the work of the NTP. Much of the ongoing Federal research is directed toward developing and validating tests for evaluating substances for immunotoxic potential. NTP has published a panel of tests for immunotoxicity testing that has been validated in the mouse. NTP continues to work on validating immunotoxicity tests in other species and on improving its current panel of tests. NTP is also applying the tests to various substances. EPA is working on developing and validating immunotoxicity tests using the rat as the test species, and has published immunotoxicity testing guidelines for certain pesticides. Immunotoxicity is a major concern of FDA researchers when evaluating new products for human and animal consumption.

Few substances have been regulated by the Federal Government on the basis of immunotoxicity. OSHA has issued regulations for eight substances on the basis of their ability to provoke hypersensitivity. FDA has restricted the use of Yellow Dye No. 5 and sulfites in foods because of their association with hypersensitivity. These agencies and EPA regulate other substances that have shown evidence of immunotoxicity in a few animal tests, but other health effects serve as the basis for those regulations.

Several Federal activities are designed to enhance public awareness of the hazards of toxic substances, including immunotoxicants. OSHA's hazard communication standard requires that workers be provided with information about known health hazards in their jobs. However, since so little information is available regarding immunotoxic effects, and since the standard cannot be used to compel testing, the standard does little at present to protect workers from immunotoxic hazards. Community right-to-know legislation requires EPA to collect information about substances that pose potential toxic hazards to local communities and make that information available to the public. As with the OSHA standard, however, this program does not permit EPA to require that health effects information be developed, therefore available information on immunotoxicity is very limited. ATSDR is disseminating information about health risks, including immunotoxicity, to the public.

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