Chapter 7

The Federal Regulatory Response

"The workplace should not be a test tube and company employees should not be guinea pigs. We cannot tolerate stone-age protections for space-age dangers. "

Senator Harry Reid
Committee on Environment and Public Works
March 6, 1989

"There are substances commonly used in the home that make our lives easier. We use these substances in good faith, seldom questioning the fact that they could cause peripheral nerve or brain damage. Consumers rely on the Government's and industries' judgment on health dangers associated with the use of chemicals and pesticides.

Representative Harold L. Volkmer
Committee on Science and Technology
October 8, 1989

"The industrial laboratory will always outpace the regulatory agency in providing substitutes for banned chemicals, and some of those substitutes in field use may prove as troublesome as the ones they replace. "

William D. Ruckelshaus
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Over the years, Congress has enacted many statutes that apply directly or indirectly to the regulation of neurotoxic substances. Some of these statutes are framed in broad terms to protect human health in general; others address specific adverse health effects, such as carcinogenicity, teratogenicity, and in rare cases behavioral changes and neurotoxicity (25). Some statutes provide broad authority for requiring that substances be tested for potential toxic effects; others require the implementing agency to prove that substances may be harmful before any regulatory action can be taken. Some statutes call for absolute protection of health and safety; others allow for balancing risks, costs, and benefits.

Not surprisingly, Federal agencies have promulgated equally diverse regulations. Some regulatory programs require substantial testing of chemicals to screen for toxic effects; others are not empowered to require any such testing. Some call for screening substances before they are allowed to enter the marketplace; others are reactive, taking effect only when evidence indicates that an existing chemical can, or does, cause harm.

Federal laws governing toxic substances can be divided into three general categories:

1. licensing and registration laws for new and existing chemicals, which entail an explicit review process and may include a requirement for toxicity testing;
2. standard-setting laws for chemicals used in specific situations, under which regulatory agencies determine recommended or required limits on toxic substances in various environmental media (air, water, or soil) or emitted by a given source, or dictate appropriate labeling of products that contain toxic substances; and
3. control-oriented measures for dealing with chemicals, groups of chemicals, or chemical processes that are explicitly identified in the laws. [1]

Distinctions among the three categories are not absolute—there is more of a continuum than a discrete grouping in the legislative language—but this classification indicates the basic types of approaches that have been developed to protect the public and the environment from the adverse effects of toxic substances. Table 7-1 presents key features of 18 Federal laws regulating the use of toxic substances (14).

The approach to regulation embodied in a statute largely determines the Federal response. Licensing programs are externally driven and must respond to petitions or applications from manufacturers or other outside parties; standard-setting and control-oriented programs may have to respond to deadlines set by Congress (for control-oriented programs, however, these deadlines generally affect regulation of sites rather than specific chemicals). Application and notification procedures under the licensing statutes require the regulatory agencies to review however many chemicals per year are submitted, whereas agencies charged with setting standards can control the scheduling and priorities of review to a greater degree.

Although some of the standard-setting and control-oriented programs have the ability to pursue research into the adverse effects of chemical substances, it is the licensing statutes that generally grant authority to require that chemicals be tested for toxic effects. As a consequence of these and other differences, implementation of licensing statutes has tended to be more active and, accordingly, more controversial than that of standard-setting or control-oriented statutes.

It is necessary to keep in mind that regulatory activities may be curtailed, expanded, or otherwise affected by various nonregulatory factors. The appropriations process determines the resources available to an agency to carry out its regulatory activities. Oversight by the Office of Management and Budget may require an agency to restrict or modify regulatory implementation. Abundant litigation challenging environmental laws and regulations has created a large body of court decisions that further interpret and clarify agencies' regulatory rights and responsibilities (see box 7-A); product

[1] Others have classified the regulatory response differently; one environmental law treatise, for example, suggests only two categories—product controls and pollution emission controls. The scheme proposed here is not definitive but is meant to emphasize how chemicals are singled out for attention and review in the legislative and regulatory processes.

Table 7-l—Key Features of Federal Laws Regulating Toxic Substances

Statute	Regulatory authority (regulatory agency)[a]	Toxic substance or effect of concern	Approach to risk
Part1-Licensing Laws			
Federal Food, Drug, and Cosmetic Act	Control levels of added substances (FDA)	"any poisonous or deleterious substance which may render it injurious to health"	No explicit consideration of benefits
	Control levels of natural components of food (FDA)	"poisonous or deleterious . . . does not ordinarily render it injurious to health"	Balance risk against need for plentiful and affordable food
	Control levels of environmental contaminants (FDA)	"poisonous or deleterious . . . does not ordinarily render it injurious to health"	Balance risk against whether required, unavoidable, or not measurable
	Set (EPA) and enforce (FDA, USDA) tolerances on pesticide residues for food and feed crops	"poisonous or deleterious . . . not generally recognized as safe for use . . . to the extent necessary to protect the public health"	Ensure adequate, wholesome, economical food supply; other ways pesticide affects consumers; usefulness
	Regulate introduction of new drugs and biologics (FDA)	"substantial evidence that safe and effective"; no "imminent hazard to public health"	Balance risks against efficacy and need
	Report on adverse reactions to drugs (FDA)	"any adverse experience ., . includes any side effect, injury, toxicity, or sensitivity reaction"	Balance risks against drug benefits
	Label cosmetics (FDA)	"poisonous or deleterious . . . may render it injurious"	No explicit consideration of benefits
Federal Insecticide, Fungicide, and Rodenticide Act	Register pesticides (EPA)	"will not generally cause any unreasonable risk to man or the environment"	Pesticide must not only be safe under conditions of use, but also effective
Toxic Substances Control Act	Require testing of existing chemicals where data are inadequate to assess risk (sec. 4); prohibit introduction into commerce of chemicals that will present an unreasonable risk (sec. 5); restrict or prevent production, use, or disposal of existing chemicals that present unreasonable risk (sec. 6) (EPA)	"unreasonable risk of injury to human health or the environment. . . including] carcinogenesis, mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects, and any other effect. . ."	Risks posed by chemical must be balanced against benefits it provides (i.e., risk must be unreasonable)
Part II-Standard-Setting **Laws**			
Clean Air Act	Conduct research on air pollution (EPA)	"adverse effects on health, including, but not limited to, behavioral physiological, toxicological, and biochemical effects"	NA
	Set air quality standards; regulate emissions of hazardous air pollutants; set standards for vehicle emissions, fuels, and fuel additives (EPA)	"endanger public health"	"Adequate margin of safety"
Federal Water Pollution Control Act; Clean Water Act	Set effluent standards for water; establish water quality criteria (EPA)	"identifiable effects on health and welfare"	Water quality criteria do not consider economic or technological feasibility
Safe Drinking Water Act	Set MCLs and MCLGs for public drinking water supplies (EPA)	"may have an adverse effect on the health of persons"	MCLGs do not consider feasibility, but MCLs do
Consumer Product Safety Act	Promulgate consumer product safety standards (CPSC)	"an unreasonable risk of injury"	Balance risks against product utility, cost, and availability
Federal Hazardous Substances Act	Ban hazardous substances for household use (CPSC)	"toxic. . . may cause substantial personal injury or substantial illness"	"the public health and safety can be adequately served"

Table 7-l—Key Features of Federal Laws Regulating Toxic Substance-Continued

Statute	Regulatory authority (regulatory agency)[a]	Toxic substance or effect of concern	Approach to risk
Federal Mine Safety and Health Act	Set standards for airborne contaminants in mines (MSHA)	"protection of life and prevention of injuries. . . material impairment of health or functional capacity"	Attain highest degree of health and safety protection; latest available scientific data; feasibility; and experience gained with health and safety laws
Occupational Safety and Health Act	Set standards for airborne contaminants in the workplace (OSHA)	"material impairment of health or functional capacity"	Attain highest degree of health and safety protection; latest available scientific data; feasibility; and experience gained with health and safety laws
Part III-Control-Oriented Laws			
Comprehensive Environmental Response, Compensation, and Liability Act; Superfund Amendments and Reauthorization Act	Fund cleanup of hazardous waste sites; designate reportable quantities for environmental release; report on community preparedness and release; prepare toxicity profiles on contaminants (EPA)	"substantial danger to the public health or welfare"	Focus on highest-risk chemicals
Controlled Substances Act	Control drugs that have potential fo rabuse (USDJ, FDA)	"substantial and detrimental effect"	Define list of substances to be controlled
Lead-Based Paint Poisoning Prevention Act	Determine, if possible, a safe level of lead in paint (CPSC)	Poisoning of children by lead-based paint	Determine whether any safe level could be established above 0.06°/0
Marine Protection, Research, and Sanctuaries Act	Regulate ocean dumping (EPA)	"adversely affect human health, welfare or amenities"	Consider appropriate alternative locations
Poison Prevention Packaging Act	Promulgate standards for packaging substances that could produce effects of concern (CPSC)	"serious personal injury or serious illness"	Determine degree and nature of hazard to children
Resource Conservation and Recovery Act	Regulate the handling of hazardous wastes; list hazardous wastes on basis of constituents (EPA)	"protect human health . . . serious irreversible or incapacitating reversible illness substantial present or potential hazard"	Control handling to minimize risks

[a]**List of acronyms** is **given** in app. F.

SOURCE: Office of Technology Assessment, 1990.

litigation may further modify the regulatory process. Furthermore, regulations may incorporate direct or indirect economic incentives in attempting to motivate industry to control pollutants (see ch. 9), adding another dimension to regulatory implementation. Clearly, the regulatory processes described herein are not rigidly circumscribed but are part of a larger regulatory dynamic (14).

LICENSING AND REGISTRATION LEGISLATION AND REGULATIONS

Three statutes govern most aspects of the licensing and registration of drugs, food additives, pesticides, and industrial chemicals: the Federal Food, Drug, and Cosmetic Act; the Federal Insecticide, Fungicide, and Rodenticide Act; and the Toxic Substances Control Act. All of these statutes require submission of applications for use of, or notification of intent to use, new chemical substances; they also authorize reviews of previously registered chemicals. The review processes followed under these acts have four basic steps:

1. manufacturer's submission of data;
2. evaluation of data by the responsible regulatory agency;
3. requests for additional data (if necessary); and
4. agency determination (which may or may not involve a formal rule-making procedure).

The extent to which neurotoxicity is addressed in the process varies among and within statutes according

Box 7-A—Toxic Substances Laws Go To Court: *The Judicial Role in Interpreting Legislative Language and Regulatory Implementation*

The passage of a statute by Congress establishes overarching boundaries for regulatory implementation, but translating Congress' goals, as stated in the legislative language, into regulatory action is by no means a simple process. Environmental laws abound with general phrases calling for protection of "public health and the environment' or for protection from 'adverse effects' some laws require that standards incorporate a' 'margin of safety. " The definition of these phrases often depends on the ever-changing forefront of scientific research into what levels of toxic substances may cause adverse effects—what, indeed, should be defined as an adverse effect—and, based on the often uncertain conclusions of preliminary research, what constitutes a margin of safety. Congress leaves the interpretation of its mandates to the discretion of the Federal regulatory agencies.

Thus, regulatory agencies get the first opportunity to interpret what Congress meant, but their responses are modified by many factors: the appropriations process; oversight by the Office of Management and Budget; requirements of the Administrative Procedures Act that the agency notify and obtain comments from the public on any proposed regulations and that it respond to all significant comments; recommendations of scientific or technical advisory panels; recognition that standards and regulations may have a profound effect on product litigation; and other internal and external pressures and requirements. It typically takes from 2 to 8 years for an agency to promulgate a rule, and the rule is then subject to further examination and interpretation through court challenges and interpretive rulings.

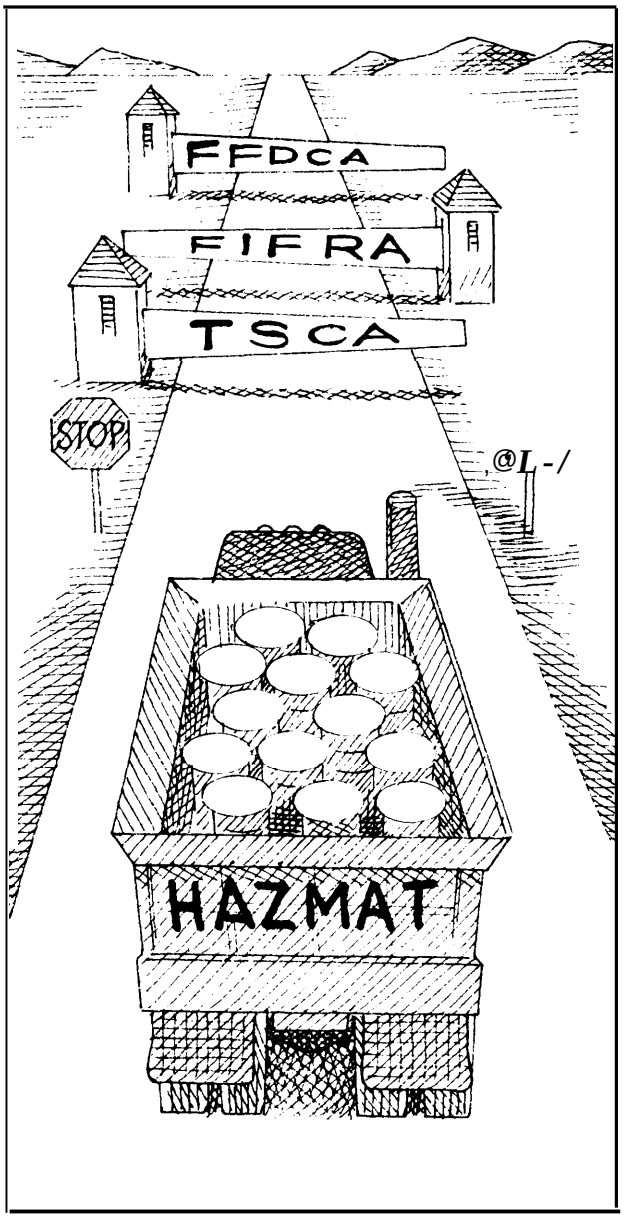
Administrative and procedural complexities have made environmental statutes the most frequently litigated of all fields of administrative law (Grad, 1985). During litigation, courts must evaluate agencies' interpretations of congressional intent, and they must often evaluate the complex underlying technical issues as well—including the definitions of adverse effects or margins of safety. The judicial interpretation may have a considerable impact on how the legislative language can be interpreted and how the regulations can be implemented.

In at least one case, the Federal district courts have upheld the use of neurotoxic effects in the setting of standards. In 1980, the Lead Industries Association, Inc., brought suit against the Environmental Protection Agency (EPA), charging that the Administrator went beyond the scope of his authority in setting standards for lead under the Clean Air Act. EPA had issued a rule setting the primary national ambient air quality standard for lead on the basis of its effects on the blood and on the nervous system (43 FR 46254). After considerable study, EPA had determined that lead's effects on the nervous system begin to appear at the level of 50 micrograms of lead per deciliter of blood (ug/dl), that anemia and other effects appear at 40 ug/dl, and that identifiable changes in the blood (though not easily diagnosed through clinical examination) begin at 30 ug/dl. To provide an adequate margin of safety, EPA set a target for the population of 15 ug/dl.

Among other arguments, the Lead Industries Association contended that the EPA's rule was not adequately supported by the finding that neurotoxic effects begin to appear at 50 ug/dl and that basing the standard on subclinical effects at 30 ug/dl went beyond the Agency's statutory authority. The courts upheld EPA's finding on neurotoxicity, stating that the record revealed ample support for the Administrator's determination of when central nervous system effects begin to occur. The decision noted that it was not the function of the court ''to resolve disagreement among the experts or to judge the merits of competing expert views. ' (" [C]hoice among scientific test data is precisely the type of judgment that must be made by EPA, not this court. That evidence in the record may also support other conclusions, even those that are inconsistent with the Administrator's, does not prevent us from concluding that his decisions were rational and supported by the record. ' The court further upheld EPA's justification for the margin of safety, noting that the legislative history of the Clean Air Act shows that margins of safety were considered essential for protecting against hazards that had not yet been identified.

Judicial interpretation is one of many factors influencing the implementation of regulations; as this case shows, it may strengthen an agency's regulatory decisions. As for neurotoxic effects, which have rarely been explicitly mentioned in statutes, the courts may play an important role in ensuring that they are considered in the process of protecting public health and the environment.

SOURCES: F.P. Grad, "A Brief Account of the Beginnings of Modern Environmental Law," Treatise on Environmental Law, sec. 1.01 (St. Paul, MN: Matthew Bender, 1985); "kid Industries Association, Inc. v, U.S. Environmental Protection Agency, " *Federal Reporter* (2d series) 647:1130-1189, 1980.



Illustrated by: Ray Driver

to the type of substance being reviewed and whether it is a new or existing substance.[2]

Federal Food, Drug, and Cosmetic Act

The earliest Federal statute governing food safety was the Food and Drugs Act of 1906 (19), which prohibited the marketing or transport of "adulterated food," that is, any food that contained "any added poison or other added deleterious ingredient which may render such article injurious to health." The Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 301-392),[3] which replaced the original Act in 1938, expanded controls to include naturally occurring as well as added toxic substances. However, it did not delineate specific toxic effects. The Act is based on a broad concept of safety as absence of injury:

> A food shall be deemed to be adulterated-if it bears or contains any poisons or deleterious substances 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 . . . [sec.* 402(a)(l)] [emphasis added].

Thus, added substances are governed by a stricter standard than naturally occurring substances. Since its passage, FFDCA has been clarified and expanded by various amendments, but the language referring to toxic effects remains the same.

The Act grants the Food and Drug Administration (FDA) authority to regulate foods, drugs, and cosmetics in the following categories:

- food and general safety (sec. 402),
- environmental contaminants (sec. 406),
- pesticide residues (sec. 408),
- food additives (sec. 409),
- drugs and biologics (sec. 505),
- cosmetics (sec. 601), and
- color additives (sec. 706).

FDA can use this authority to require premarket submission of specific toxicity test data. It could incorporate neurotoxicity tests in the guidelines for recommended testing or require neurotoxicity testing during the application process if there is evidence of potential neurotoxic effects.

Environmental Contaminants of Food

FDA is authorized to regulate unavoidable contaminants of raw agricultural commodities under" either the general food safety provisions (sec. 402) or the specific provisions of section 406, which calls for FDA to:

[2]The information in this section is drawn primarily from personal communication with officials at the respective agencies.

[3]All United States Code (U. S. C.) citations refer to the 1982 edition, unless otherwise noted.

> . . . promulgate regulations limiting the quantity therein or thereon to such extent as. . . [is] necessary for the protection of public health, and any quantity exceeding the limits so fixed shall also be deemed unsafe . . . (21 U.S.C. 346).

In setting the limits, FDA must consider whether the substance is required or unavoidable in the production or processing of the food item and the potential effects of the substance on health. Though not included in the statute, the extent to which the substance can be detected in foods is also considered, since it would be impossible to enforce limits that could not be detected (19).

FDA asserts that it is not always appropriate to set formal tolerance levels for contaminants-e.g., when new toxicity data are being developed for a substance that previously had little or none (39 FR 42745). In addition, the formal rule-making procedure demanded for setting tolerances is elaborate and time-consuming. Given these circumstances, FDA has chosen to rely primarily on a regulatory option not explicitly established by statute—that of setting informal tolerances, called action levels. An "action level is based on the same criteria as a tolerance, except that an action level is temporary until the appearance of more stable circumstances makes a formal tolerance appropriate" (39 FR 42745).4 Action levels are not binding, nor do they have the legal force of tolerance levels, but they can be used to "prohibit any detectable amount of the substance in food" (21 CFR part 109.4). Any food that contains more than the action level dictates may be declared adulterated and be subject to further regulatory action.

In establishing either an action level or a tolerance, FDA uses available information on health effects to determine a dosage at which risk of exposure to a contaminant is acceptable. Once the action level or tolerance is established, FDA may take appropriate action to restrict food that does not meet these standards.

Pesticide Residues

The 1954 amendments to FFDCA empowered FDA to set and enforce standards for pesticide residues on raw, unprocessed agricultural commodities. More recent amendments bestowed the standard-setting responsibility on the Administrator of the Environmental Protection Agency (EPA):

> The Administrator [of EPA] shall promulgate regulations establishing tolerances with respect to the use in or on raw agricultural commodities of poisonous or deleterious pesticide chemicals and of pesticide chemicals which are not generally recognized . . . as safe for use, to the extent necessary to protect the public health [sec. 408(b), 21 U.S.C. 346a, 1976)].

Pesticides that are expected to become more concentrated during processing require separate tolerances. EPA may revoke or change tolerances if new evidence or further review indicates that a change is necessary (29).

The establishment of tolerances takes place concurrently with pesticide registration under the Federal Insecticide, Fungicide, and Rodenticide Act, described below. The manufacturer petitions EPA to set a tolerance for the pesticide residue; the pesticide cannot be registered for use on a food or feed crop until a tolerance has been set or an exemption granted (48). The FFDCA specifies that a pesticide tolerance petition include "full reports of investigations made with respect to the safety of the pesticide chemical" [sec. 408(d)(l)(C)], thus placing the burden of proof of the safety of a pesticide on the manufacturer.

Food and Color Additives

The Food Additives Amendment of 1954 (Public Law 85-929) sought to "prohibit the use in food of additives which have not been adequately tested to establish their safety. " The amendment initiated an application process for the approval of food additives that, like the pesticide tolerance provisions, shifted the burden of proof from the FDA to the producer.

Manufacturers must file a written petition before a potential food additive can be approved for use. The petition must contain "scientific data adequate to support safety" (15) and ". . . full reports of investigations made with respect to the safety for use of such additive, including full information as to the methods and controls used in conducting such investigations' [sec. 409(b)(2)(E)].

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[4]Recent court challenges, however, have resulted in a decision requiring FDA to subject proposed action levels to public notification and comment; FDA incorporated the decision in a proposed rule in April 1989 (54 FR 16128-30). It remains to be seen whether action levels will continue to offer a streamlined alternative to the setting of tolerances.

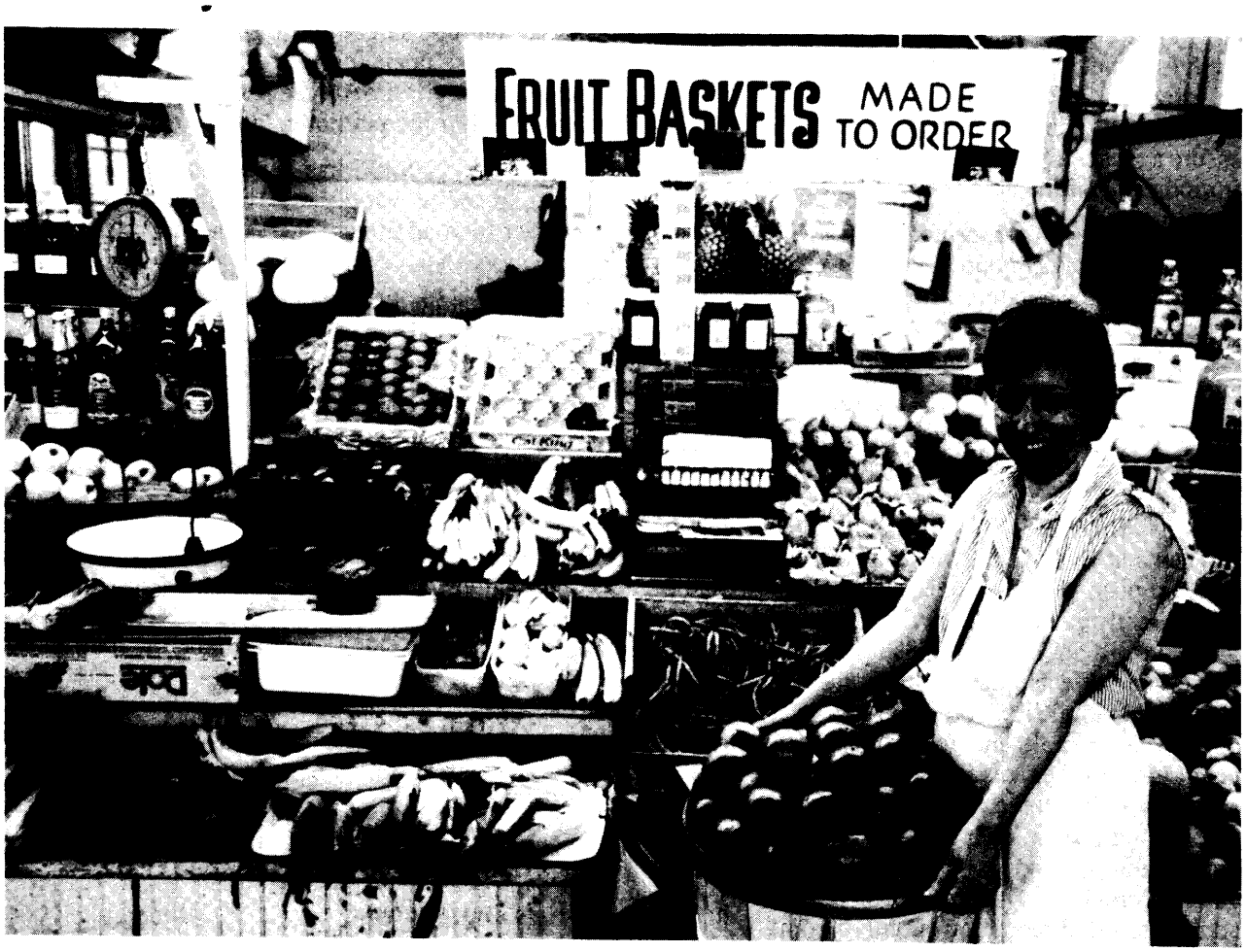

Photo credit: U.S. Environmental Protection Agency

FDA decides whether, and in what amounts, a food additive may be used on the basis of the data submitted with the application. It has drawn its interpretation of safety from the legislative history of the Act, which used the phrase "reasonable certainty of no harm," and has incorporated that standard into its regulations regarding toxicity testing (15).

Color additives to food are regulated under the Color Additive Amendments of 1960. These regulations are essentially the same as those for food additives, including a process of premarketing approval. In addition, color additives to drugs and cosmetics are regulated. A color additive may be approved for general or restricted use if it is found that "it is suitable and may be safely employed" [sec. 706(b)(2)].

Petitions for approval of food and color additives are handled by FDA's Center for Food Safety and Applied Nutrition (CFSAN). These include direct food additives (e.g., preservatives) and color additives, as well as indirect additives, such as constituents of packaging materials that might migrate into food. Although the application process officially begins with submission of the petition and supporting data, CFSAN may, and frequently does, hold informal preapplication meetings with petitioners to clarify data needs.

Each application must contain all data relevant to assessing safety. The tests required are determined on the basis of predicted exposure. For direct food additives, CFSAN test guidelines, known as the Red Book, list particular exposure levels and characteristics of chemical structure that require certain types of tests (30). Most substances must be subjected to subchronic studies in mammals as well as reproductive tests. No specific neurotoxicity tests are required, but the protocols do call for observation of

effects on animal behavior, so some prediction of adult or developmental neurotoxicity, or both, may be provided. The test requirements are negotiable, but the petitioner must present sufficient data to ensure a reasonable certainty that no harm will result from the use of the additive.

The Red Book is currently being revised, and the new version may contain specific tests for neurotoxicity. The precise nature of these tests is still under review. In order for FDA to impose any additional testing requirements, it must show that further tests are necessary.

Petitions must be reviewed within 90 days of submission, although FFDCA permits extensions to 180 days. Each petition is evaluated by senior scientists from CFSAN's Division of Toxicological Review and Evaluation. Most reviewers are general toxicologists; the division has had neurotoxicologists directly involved in reviewing petitions in the past, but few in 1988 or 1989. If the data indicate neurotoxic effects, the division may call on the Neurobehavioral Toxicology Team-neurotoxicologists who are not generally members of the review team-for further research. This team has been asked to review three chemicals in the last 5 years; the total number of chemicals reviewed by CFSAN during that period is uncertain, but the center annually reviews approximately 60 indirect food additives, 10 direct food additives, and 10 color additives.

If the toxicological data submitted with a petition are insufficient for reaching a conclusion on whether a substance poses unreasonable risks, CFSAN negotiates with the petitioner to conduct additional tests. New data must be submitted within 180 days, although extensions may be given for reasonable cause. (Time spent on developing new data is not counted in the time limit by which FDA must act on the application, and if the necessity for new information is a result of the petitioner's failure to submit all data that were clearly required, the FDA may reset the clock to day 1 when the additional data are submitted.)

If CFSAN determines, on the basis of toxicological data and potential exposure patterns, that a substance may be harmful, the food or color additive petition may be denied. Alternatively, FDA may impose limits on the amount of additives that will be allowed in foods. If the petition does not contain enough evidence for CFSAN to make a determination on the safety of a substance[a], and if the petitioner is unable or unwilling to develop the necessary data, CFSAN requests that the petition be withdrawn or the petition is denied approval.

To date, CFSAN has reviewed the neurotoxic potential of a variety of direct food additives, indirect food additives, and color additives, including:

- acrylamide (as a contaminant of polymer food contact surfaces),
- acrylonitrile (as a contaminant of polymer food contact surfaces),
- aspartame (artificial sweetener),
- chlorofluorocarbons (Freon 12),
- cyclamates (artificial sweeteners),
- erythrosin (FD&C Red No. 3),
- methyl chloride (as solvent for hop extract),
- methyl tin compounds (as stabilizers for plastics),
- organophosphites (antioxidants in food packaging):
  -di-tert-butylphenyl phosphite,
  --octadecyl phosphite, and
  —Tris phosphite.

As noted above, the Neurobehavioral Toxicology Team does not regularly participate in such reviews.

Drugs and Biologics

Drugs are regulated under various categories, including new drugs (for humans), biologics (biological products such as vaccines), and animal drugs. The statute requires submission of a new drug application (NDA) before a drug can be approved for market. The NDA must contain "substantial evidence" that the drug is both safe and effective:

> . . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed . . . [sec. 505(d)(7)].

This is generally considered to be the highest standard for drug approval in the world.

The statute also provides that FDA shall not approve a drug if it finds deficiencies in the safety tests conducted or if the test data indicate a lack of

safety. If clinical investigations "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof or if "the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions,' FDA is directed to refuse the application [sec. 505 (d)(1) and (2)].

FDA may deny approval of a new drug on the finding of "an imminent hazard to the public health" [sec. 505(e)]. If the application is approved, FDA specifies how the drug is to be packaged, labeled, and so on. New drugs that are identical to previously approved drugs are subject to an abbreviated application process.

Biologics, including "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, allergenic product, or analogous product" (42 U.S.C. 262), are under the purview of a complex regulatory mechanism combining provisions of both FFDCA and the Public Health Service Act. Because they are also defined as drugs, most biologics must be tested and approved by the same process FDA uses for new drugs (29).

Animal drugs are approved under essentially the same process as human drugs, with the additional provisos that FDA must consider "the probable consumption of such drug and of any substance formed in or on food because of the use of such drug' and the 'cumulative effect on manor animal of such drug" [WC. 512(d)(2)(A)].

FFDCA also requires reporting of adverse drug reactions, both during the application process [sec. 505(i)] and after a drug has been approved [sec. 505@]. "Adverse reactions" are defined by FDA as

> any adverse experience associated with the use of a drug, whether or not considered drug-related, and includes any side-effect, injury, toxicity, or sensitivity reaction, or significant failure of expected pharmacological action" (21 CFR 310.301). This requirement for reporting adverse reactions could be used to gauge the effectiveness of the drug approval process.

Applications for approval of new or investigational prescription drugs are handled by FDA's Center for Drug Evaluation and Research; biological products are handled by the Center for Biologics Evaluation and Research. The approval process for a new drug generally takes about 3 years, but it can take up to 7 years. (The shortest approval time to date, for azidothymidine (AZT), used to treat AIDS, was 7 months.)

An NDA must contain data from all prior preclinical (animal) and clinical (human) studies. Clinical studies are conducted in three phases. Phase 1 consists of short-term tests designed to elucidate how the drug is metabolized in humans, to obtain basic pharmacological and toxicological data in humans, and, if possible, to find evidence that the drug is effective in humans. Phase 2 tests are the initial controlled clinical trials and studies of short-term side-effects. Phase 3 generally consists of controlled and uncontrolled clinical trials in a larger group of subjects. These trials are intended to provide the additional information on safety and effectiveness needed to determine the risk-benefit ratio of the drug and to draft appropriate labeling.

All drugs that have not been previously tested in humans, or for which additional clinical data are required before NDA submission, must submit an investigational new drug (IND) application before the sponsor can initiate clinical trials. New drugs that have previously undergone clinical trials, such as drugs that have been approved in other countries, may skip the IND application (if they have already been subjected to adequate, well-controlled clinical trials).

FDA has developed guidelines for the types of nonclinical studies that are needed to support approval of different types of clinical trials. The guidelines do not, for the most part, call for specific tests for toxic effects (the prevailing view at the Center for Drug Evaluation and Research is that rigid test guidelines rapidly become obsolete and may lead to false assurance of the safety of a drug). Instead, the guidelines allow for considerable latitude in the selection of test protocol. The final selection of test protocols requires that the petitioner convince FDA that the data are adequate and that FDA convince the petitioner that its requirements are not unreasonable.

An IND is reviewed by a general toxicologist. Drugs that are not designed to cause neuropharmacological effects are not necessarily reviewed separately for neurotoxicity, although behavioral effects are evaluated in animal reproduction studies and neuropathology is conducted as part of the sub-

chronic studies required for the IND. A specific review for neurotoxicity is initiated only if there is cause for suspicion. Outside experts may be called in for such reviews through mechanisms such as standing committees and special review committees. Drugs that are designed to act on the nervous system—i.e., neuroeffective substances—are reviewed separately by neurotoxicology specialists from the Division of Neuropharmacological Drug Products of the Center for Drug Evaluation and Research's Office of Drug Evaluation I.

After the phase I tests have been concluded, the applicant must conduct appropriate additional nonclinical toxicity tests. The data required hinge on the particular clinical trial under consideration. A l-year animal study incorporating ophthalmological examinations and behavioral observations is required for all drugs. (For a drug to be prescribed to women of childbearing age, reproductive toxicity studies are routinely conducted; the reproductive studies may provide some evidence regarding the potential teratological effects of the drug.)

Positive evidence of toxic effects can lead to termination or modification of the clinical trials, depending on the nature of the evidence, the seventy of the effects, and the disease that the drug is intended to treat. If the animal data included in either the IND application or NDA are inadequate, FDA will issue a "clinical hold" order to delay further clinical testing until the appropriate preclinical data are developed.

Postmarked monitoring of drugs occurs through FDA's spontaneous adverse report monitoring system. Any person observing an adverse reaction associated with the use of a drug may submit a Drug Experience Report (form FDA-1639) directly to FDA or to the drug's manufacturer, who, in turn, is required to report the information to FDA (21 CFR 1989 ed. 314.80). About 90 percent of the adverse reports FDA now receives are obtained through manufacturers and 10 percent through direct reports. Analysis of these reports constitutes FDA's device for monitoring the adverse effects of prescription drugs, including effects not noted during premarket tests or clinical trials. However, as described in box 7-B, the system is limited in many respects.

No specific neurotoxicity tests are required for drugs that are not expected to be neuroeffective. Some FDA scientists believe that it is more appropriate to conduct general preclinical toxicological tests than to focus on specific tests. FDA scientists do not appear to have reached a consensus regarding the validity of preclinical neurotoxicity tests as predictors of clinical effects. They argue that it is difficult to design clinical trials that test specifically for neurotoxic effects.

Cosmetics

Substances used in cosmetics are subject only to the "may render it injurious" clause (sec. 601 of FFDCA). FDA cannot require any toxicity testing. It can, however, require that any cosmetic product that has not been adequately tested be packaged with a warning label stating that 'the safety of this product has not been determined" (21 CFR ed. 740.10). FDA has restricted or prohibited the use of fewer than 20 ingredients on the finding that they were "poisonous or deleterious" (21 CFR ed. 700.11,21 CFR ed. 250.220) (29).

Proposed Amendments

Among the proposed amendments to the FFDCA that have been introduced during the 10lst Congress, the Food Safety Amendments of 1989 (identical versions were introduced in the House and Senate as H.R. 1725 and S. 722, respectively) are potentially relevant to toxic substances regulation. A key provision of these bills is an attempt to define a standard of "negligible risk" that would apply to pesticide residues on food without regard to balancing costs and benefits. This definition would replace the current approach, under which pesticide tolerances for both raw commodities and processed foods are set at a level to protect the public's health unless the pesticide is a carcinogen, in which case no detectable amount is allowed in processed foods. Hearings have been held on the bills, but neither has been voted on by the full assembly.[5] If passed, the negligible risk provisions—and the absence of authority for cost-benefit analyses-could have far-reaching consequences in the regulation of pesticide residues.

Federal Insecticide, Fungicide, and Rodenticide Act

FIFRA was enacted in 1947 to replace the 1910 Federal Insecticide Act. FIFRA expanded the con-

[5] As of February 1990.

Box 7-B—Limitations of FDA's Postmarked Monitoring System for Adverse Drug Reactions: Halcion, A Case Study

Halcion, the most widely prescribed sleeping medication in the United States, was first approved for use in late 1982 with a recommended usual adult dose of 0.25 to 0.50 mg. Its package insert included mentions of amnesia, confusion, agitation, and hallucinations as possible side-effects. Over the next few years, FDA's adverse reaction monitoring system recorded an excess of adverse reports for Halcion in comparison to other benzodiazepine hypnotics-even after correcting for market share of the drug. In 1987, as a result of the reports and the apparent dose-relatedness of some adverse effects, several labeling and marketing changes were made. The usual adult dose was changed to 0.25 mg, two paragraphs mentioning the apparent dose-relatedness of some side-effects were added to the package insert and a "Dear Doctor" letter was issued detailing the labeling changes. In early 1988, Upjohn, the manufacturer, discontinued the 0.50 mg tablet.

Following these changes, public concern about possible problems associated with Halcion use increased, largely because of a September 1988 article in *California Magazine* and a story on the ABC television program 20/20 in February 1989. The number of adverse reports received, which was expected to decline as a result of the labeling changes and Halcion's status as an "older" drug (the number of adverse reports associated with a drug normally decreases over time), rose. In September 1989, FDA convened an expert panel to review the reporting data on Halcion and to discuss whether further changes should be made in the labeling or marketing of the drug.

Discussion at that meeting illustrates the difficulties of drawing conclusions from the spontaneous adverse reporting process. In a comparison of adverse reports for Halcion (45 million prescriptions written since 1982) with adverse reports for Restoril (35 million prescriptions written since 1980), a drug prescribed to patients with similar sleeping problems, the following data were presented:

	Total number of reports received by FDA	
Adverse event	*Halcion*	*Restoril*
Amnestic events	267	4
Hallucinations, paranoid behavior	241	12
Confusion and delirium	304	17
Hostility and intentional injury	48	2

Overall, an average of 38 adverse reports per million prescriptions was received for Halcion, while 7.5 adverse reports per million prescriptions were received for Restoril.

These seemingly dramatic results, however, were tempered by myriad complicating variables, The influence of publicity, differences in reporting rates by manufacturers, lack of dosage information in about one-half of the adverse reports for Halcion, and "new drug" v. ''older drug' effects all obscured the significance of differences between the sets of data, The 4-week period following the 20/20 episode, for example, produced twice as many adverse reports for Halcion as the 4-week period preceding the show. The FDA panel finally concurred that the data were too unreliable to warrant action, except possibly in the case of amnesia.

The unreliable data generated by the postmarketing monitoring system now in place effectively limit FDA review to premarket trials. Unexpected interactions with other medications or long-term side-effects may easily be missed. This is particularly disturbing from the standpoint of neurotoxicity, since drugs not expected to have neuropharmacological effects are not necessarily subjected to specific neurotoxicity testing. Changes which could improve the present system might include a requirement that all adverse report forms be sent directly to FDA as well as a requirement that physicians submit reports for all ''serious" adverse reactions observed.

Because of the inherent limitations in FDA's drug approval and adverse reaction monitoring systems, it is important that physicians and patients be aware of the possible adverse effects of the medications they prescribe and consume. Drugs are approved for use under certain conditions and at certain doses, and complicating factors such as age, other medications, or illness may significantly alter the effects of these drugs. In most cases, the decision to take any medication is a personal choice for the patient; an individual cannot make an informed decision without access to information about potential adverse effects.

SOURCES: U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Psychopharmacological Drugs Advisory Committee, *Transcript of Proceedings, Thirty-First Meeting* (Rockville, MD: September 1989); "When Sleep Becomes a Nightmare," 20/20, ABC, Feb. 17, 1989; Pharmaceutical Data Services, ''Top 200 Drugs of 1989,' *American Druggist,* in press.

sumer protection aspects of the earlier statute by instituting a premarket registration procedure for all pesticides in interstate commerce. The 1972 amendments—the Federal Environmental Pesticide Control Act (Public Law 92-516)—shifted the emphasis from consumer protection to the protection of public health and the environment (47). Amendments in 1975 (Public Law 94-140), 1978 (Public Law 95-396), 1980, and 1988 refined the regulatory procedures embodied in the legislation but maintained the focus, namely, to govern pesticide use to prevent "unreasonable adverse effects. " FIFRA uses a broad standard for adverse effects:

> . . . *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 [sec. 2(bb)] [emphasis added].

The statute prohibits the sale or distribution of any pesticide in the United States unless it is registered or exempt from registration under FIFRA. It gives EPA considerable authority to require submission of data, including neurotoxicity tests, as part of the registration process for new and existing chemicals. The statute places the burden of proof of safety on the manufacturer, although in the case of existing pesticides, EPA may have to go to considerable lengths to prove the inadequacy of data before it can call for further data or regulatory action.

Photo credit: National Archives

New Pesticide Registrations

FIFRA calls for premarket review and registration of both new pesticides and pesticides with new active ingredients.[6] A pesticide may be registered if EPA determines that, when considered with any restrictions on use:

- its composition is such as to warrant the proposed claim for it;
- its labeling and other material required to be submitted comply with the requirements of the Act;
- it will perform its intended function without unreasonable adverse effects on the environment; and
- when used in accordance with widespread and commonly recognized practice, it *will not generally cause unreasonable adverse effects on the environment [sec. 3(c)(5)]* [emphasis added].

The 1972 amendments enabled EPA to require that manufacturers submit whatever data EPA specifies for approval or continuation of the registration:

> The Administrator shall publish guidelines specifying the kinds of information which will be required to support the registration of a pesticide . . . [sec. 3(c)(2)(A)].

Applications for pesticide registration are submitted to EPA's Office of Pesticide Programs (OPP). The applicant must demonstrate that anew pesticide will be both safe and effective under the proposed conditions of use. In order to demonstrate efficacy, applicants must obtain an Experimental Use Permit (EUP) to conduct field studies. (An EUP application

[6]Inert ingredients—those parts of the pesticide formulation not claimed to have anypesticidal activity-have not traditionallybeen included in the registration process. EPA has recently begun to review and evaluate them, however. Although EPA believes that FIFRA provides the authority to require testing of inert ingredients of known toxicity, it is not clear how inert ingredients of unknown toxicity should be handled (l).

requires less extensive toxicity data than the registration application, but the applicant must provide enough information to establish that the field test itself is safe.) EUPs are also obtained for new uses of a pesticide, such as application on a new crop. If the pesticide is intended to be used on food or feed crops, the applicant submits a petition for the setting of tolerances, which is done in tandem with the registration process.

The toxicity data in each application are reviewed initially by a toxicologist from OPP's Hazard Evaluation Division. The division has a neurotoxicologist on its staff who may be consulted if necessary, but the neurotoxicologist does not automatically participate in application reviews. Under division procedures, a single toxicologist is responsible for reviewing each application. The review is conducted in accordance with procedures codified in OPP's Standard Evaluation Procedures or Risk Assessment Guidelines, or both. Limited neurotoxicity testing is required only for organophosphorous pesticides, but subchronic tests include a limited evaluation of behavioral and pathological effects on the nervous system.

If data provided with an application are determined by EPA to be inadequate for a reasonable evaluation of potential hazards, the Agency will require additional toxicity testing. EPA may require tests in addition to those specified in the test guidelines, if necessary, to clarify issues raised by the data presented.

If OPP finds that a new pesticide presents an unreasonable risk of adverse effects, EPA may deny the registration altogether, restrict use of the pesticide to certain crops or to certain geographical areas, or require that it be applied under the supervision of certified applicators or that protective equipment be worn during application. In addition, EPA may impose specific labeling requirements (see box 7-C).

The FIFRA test guidelines (40 CFR ed. 158) contain very limited recommendations for neurotoxicity testing. At the present time, only organophosphates must be tested for neurotoxic effects, and they are subject to just a single type of test—a hen test for delayed neuropathy (see ch. 5 for more information on test procedures). Current guidelines require limited neuropathological examinations and observations for behavioral effects as part of acute and subchronic toxicity studies. However, the test guidelines are now under revision, and new neurotoxicity test requirements are likely to be added (the development of new guidelines is described below in the section on "new initiatives"). A review of new active ingredients registered in the past 5 fiscal years revealed that out of 54 pesticides, including 20 insecticides, only 3 were organophosphates.

Reregistration of Existing Pesticides

Because many pesticides were registered on the basis of toxicity data that might now be considered inadequate, EPA is reexamining the safety of registered pesticides. EPA may call for the registrant to develop new data for evaluating toxic effects of the pesticide. Section 3(c)(2)(B) of FIFRA states:

> . . . If the Administrator determines that additional data are required to maintain in effect an existing registration of a pesticide, the Administrator shall notify all existing registrants.

In conjunction with the FIFRA reregistration process, EPA is also mandated by FFDCA to set tolerances for the maximum pesticide residues allowed in or on various food and animal feed crops. EPA may periodically review previously set tolerances, which are enforced by FDA and the U.S. Department of Agriculture (USDA) (48 FR 39499). As pesticides go through the reregistration process, EPA may decide that the tolerance levels need to be reassessed.

Reregistration of existing pesticides does not require the submission of applications or data. Rather, OPP initiates the process by reviewing available data from its internal files and, on rare occasions, from the published literature. In the past, EPA has selected and scheduled reviews of chemicals with few restrictions, producing approximately 25 registration standards (the document which specifies the conditions that a registrant must meet to maintain the registration of a pesticide) per year. The 1988 amendments to FIFRA mandated that EPA review 600 active ingredients of existing pesticides by 1997 (i.e., more than 60 registration standards per year-a considerably faster rate than current operating procedures have fostered). EPA, therefore, is developing procedures for conducting reregistration reviews more quickly and is determining whether additional personnel will be required.

The evaluation process is similar to that for new chemicals and the test guidelines for re-registration are the same as those for registration. OPP may consult with outside experts about what kinds of

Box 7-C—Regulatory Requirements for Labeling: How Effective Are They?

Labeling requirements are a common regulatory tool for dealing with toxic but useful substances. Pesticides, prescription and over-the-counter drugs, household substances, and all commercial poisons are subject to labeling provisions incorporated in statutes such as the Federal Insecticide, Fungicide, and Rodenticide Act; the Federal Food, Drug, and Cosmetic Act; the Federal Hazardous Substances Act and the Consumer Product Safety Act.

Labels are intended to reduce the risks of exposure to, or harm from, toxic substances by alerting consumers to the dangers of a substance and providing instructions for its safe and proper use. When regulators make decisions contingent on specific labeling requirements, they rely on at least three tacit assumptions: 1) that consumers will read the label; 2) that they will understand and believe it; and 3) that they will obey its instructions. Clearly, all three must happen in order for labels to be effective in preventing dangerous exposures. But is it realistic to rely on labels?

Increasing evidence suggests that it is not. An Environmental Protection Agency (EPA) draft report on the effectiveness of pesticide labeling finds several weaknesses in current schemes. The report which includes a survey of representatives from the pesticide industry, State regulatory agencies, environmental organizations, and household users, found that few people read an entire label and that many people may not even read the parts of the label that relate specifically to their intended use of the chemical. Labels maybe redundant and too technical; the information is often crowded and difficult to read; and the instructions may be vague or contradictory. (For example, the label on one rat poison instructed users to keep the poison away from wildlife.) Furthermore, there are few guidelines on how to label for specific toxic effects, such as neurotoxicity, EPA concluded that many labels are not well designed for their audiences and must be improved if they are to have any real effect.

What is the solution? EPA suggests measures such as greater use of hazard symbols, more readable and perhaps standardized formats, and a uniform system of designating hazards so that consumers can recognize them more easily. EPA is developing criteria for the labeling of specific categories of toxic effects, including neurotoxicity; guidelines may be issued by early 1990.

Labeling requirements have often been central in product litigation cases. Court decisions have stressed the need for labeling to protect humans from injury, and one State court ruled that even ''compliance with Federal labeling requirements will not prevent the finding that the manufacturer had not fully disclosed the risks of a product" (Grad, 1985), It appears, then, that industry also stands to benefit by working with regulators to develop adequate and effective labels.

SOURCES: U.S. Environmental Protection Agency, "Pesticide Label Utility Project Report, " unpublished draft, April 1986; F.P. Grad, ''Pesticide Pollution-Labeling and Misbranding,' *Treatise on Environmental Law*, *sec. 8.03.4* (St. Paul, MN: Matthew Bender, 1985).

additional data should be developed. If additional data are needed, EPA issues a data call-in, either through publication in the Federal Register or by sending letters to affected registrants. FIFRA grants EPA the authority to request any additional data that are determined to be necessary.

If EPA determines during the reregistration process that an existing pesticide ingredient may pose an unreasonable risk, the chemical may undergo a special review as described below. If registrants do not respond to the data call-in (as is generally the case for pesticides that are no longer being manufactured), the registration is canceled. If, in the course of reregistering a pesticide, EPA finds that it poses an unreasonable risk, the Agency may cancel or suspend the chemical without initiating a special review.

EPA has requested specific neurotoxicity test data in a number of cases. While the Agency's database on registration standards does not enable investigators to determine all chemicals for which neurotoxicity data call-ins have been issued, it does include a data call-in (under consideration) to evaluate nervous system lesions that may be induced by thiocarbamates and a developmental neurotoxicity study protocol on N, N-diethyl-m-toluamide (Deet), the active ingredient in many mosquito repellents.

Active ingredients of existing pesticides undergo special review if EPA finds that they may pose an unreasonable risk of adverse effects. The special review is a formal procedure; accordingly, a notice of the initiation of the review and of each subsequent step in the process must be published in the Federal Register.

The review begins with an evaluation by EPA staff similar to that conducted for the registration of a new pesticide. In addition, EPA's independent Science Advisory Panel examines each case, and the Agency seeks public comment as part of the rule-making process. If a data call-in has not already been issued, EPA may issue one at this time. EPA can request all data relevant to the question of whether a chemical poses unreasonable risks of adverse effects.

If EPA determines that the risks of a pesticide outweigh the benefits of its continued use, it may cancel or suspend registration of the pesticide or impose restrictions on its registration. Registration may be suspended during the time it takes to complete the cancellation proceedings if EPA determines that the risks of use during that time outweigh the benefits. A suspension may be appealed and public hearings requested. EPA may also issue an emergency suspension, which is immediate and absolute and cannot be appealed. Other potential restrictions are the same as listed above for new pesticide registrations. Until 1988, EPA was required to indemnify all manufacturers and consumers for any amounts of the pesticide they possessed, which made cancellation proceedings extremely costly for pesticides that were being marketed in significant quantities. Now, however, EPA must reimburse only endusers (usually farmers).

Photo credit: U.S. Environmental Protection Agency

About 14 special review decisions are made each year, one-third of which are final decisions to initiate special review. Five active ingredients are known to have been reviewed for neurotoxicity. On further review, three of these, dichlorvos, tributyl phosphorotrithioate, and S, S, S-tributyl phosphorotrithioate, were returned to the registration process and two, acrylonitrile and EPN (phenylphosphonothioic acid, o-ethyl, o-p-nitrophenyl ester), were not (9). Registration of acrylonitrile was voluntarily canceled; EPA imposed restrictions (protective clothing and new labeling requirements) on the use of EPN (phenylphosphonothioic acid, o-ethyl, o-p-nitrophenyl ester), and subsequently all registrations were voluntarily canceled. Aldicarb, which has well-documented neurotoxic effects, is subject to special review, but the principal focus of the special review is the potential of Aldicarb to contaminate groundwater. No chemical has undergone full special review for neurotoxicity.

Approximately 75 active pesticide ingredients are on EPA's restricted use list (i.e., they may only be used under the supervision of a certified applicator), some of which are restricted because of concern about their neurotoxic effects. While there are certainly active ingredients whose use is restricted based on their neurotoxic effects (48 FR 39496), determining which ones was not feasible within the limits of this survey.

Toxic Substances Control Act

The Toxic Substances Control Act (TSCA) (Public Law 94-469) was enacted in 1976 to "regulate commerce and protect human health and the environment by requiring testing and necessary use restrictions on certain chemicals. " Congress intended to create "adequate authority" to test and regulate chemicals in commerce that are not subject to other statutes:

> [A]dequate authority should exist to regulate chemical substances and mixtures which present an

> *unreasonable risk of injury to health or the environment,* and to take action with respect to chemical substances and mixtures which are *imminent hazards. . . [sec.* l(b)(2)] [emphasis added].

TSCA defines several health and environmental effects of concern, including neurotoxic effects that are exhibited as behavioral disorders:

> The health and environmental effects for which standards for the development of test data may be prescribed include carcinogenesis, mutagenesis, teratogenesis, *behavioral disorders,* cumulative or synergistic effects, and any other effect which may present an unreasonable risk of injury to health or the environment [sec. 4(b)(2)(A)] [emphasis added].

The statute, which is one of the most procedurally complex pieces of legislation in the area of human health and the environment, sets forth a framework that authorizes EPA to review the safety of existing chemicals, to receive premanufacture notices (PMNs) for new chemicals, to regulate hazardous substances, and to call for the reporting of data on health and environmental effects and substantial risks. EPA may, in some cases, require that manufacturers conduct health and safety studies, but the burden of proof is on the Agency to find that a chemical substance or mixture may or will present an unreasonable risk to public health or the environment.

Photo credit: U.S. Environmental Protection Agency

New Chemicals

TSCA requires manufacturers to notify EPA in advance of the intended introduction into commerce of a new chemical (through PMNs) or the intended manufacture or processing of any chemical for a significant new use. (The Act does not require PMNs for the production of small quantities of chemicals for the purpose of research and development.) Submitters are required to present all test data that indicate whether "the manufacture, processing, distribution in commerce, use, and disposal of the chemical substance or any combination of such activities will not represent an unreasonable risk of injury to health or the environment" [sec. 5(b)(2)(B)(i)].

EPA has 90 days (extendable under certain circumstances to 180 days) to review the PMN. If EPA determines that the chemical may present an unreasonable risk, it may prohibit or limit the use of the chemical in commerce until data are developed to permit a further evaluation of the chemical's effects. If EPA decides that a substance "presents or will present" an unreasonable risk, it may restrict or prohibit the production, use, or disposal of the substance.

The PMN contains data on a chemical's identity and structure, proposed use, byproducts, and impurities and is submitted to EPA's Office of Toxic Substances (OTS). Certain chemicals are also subject to reporting under a significant new use rule (SNUR); EPA must be notified if such a chemical is to be used in a way that differs significantly from that proposed in the original PMN (usually because the evaluation of the PMN depended on a specific pattern of use).

Because TSCA does not require that manufacturers carry out any specific program of toxicity testing in order for new chemicals to be approved, PMNs are rarely submitted with toxicity data—fewer than 50 percent of all PMNs and fewer than 65 percent of PMNs for nonpolymers contain any toxicity data(5). PMNs that do include toxicity data generally provide results from a minimal set of studies, perhaps two or three acute tests and maybe a test for irritation (see ch. *5* for details on testing). **The requirement for manufacturers to submit all data in their possession may act as a disincentive to testing, in**

that evidence of toxicity could lead EPA to conclude that there may bean unreasonable risk, whereas the absence of data will not do so.

Because the PMN generally provides few data, most evaluation is performed on the basis of the structural analogues of the new chemical to existing chemicals and extrapolations from known properties of well-characterized chemical classes. Thus, the first stage of the PMN review is a computer-assisted search for structural analogues with known toxicity (or lack of toxicity). Senior OTS toxicologists with expertise in various specialty fields then review the chemical's potential toxicity. Their review is based on the structure-activity relationships revealed by the computer search and conducted by members of the review team. Until recently, neurotoxicologists were not routinely present at the initial structure-activity meetings but were called on afterward if concerns about neurotoxicity were raised. Under current OTS procedures, a neurotoxicologist is present at the initial structure-activity review and all appropriate meetings thereafter.

Unlike the public regulatory process for reviewing existing chemicals, the PMN process rarely calls on reviewers outside of OTS. In addition, because of the high proportion of confidential business information that accompanies PMNs, little of the review process is open to the public (see box 7-D).

If toxicity is predicted on the basis of structural analogues, a chemical may be submitted to standard review, a detailed examination that consumes much of the time allotted for the PMN review. From fiscal year 1984 through fiscal year 1987, approximately 20 percent of the 6,120 PMN chemicals received a detailed review. Based on the standard review, EPA has concluded that approximately 10 percent of all PMN chemicals may or will present unreasonable risks of adverse effects on human health or the environment.

EPA cannot require additional toxicity data unless it finds that a chemical mayor will present unreasonable risks. However, EPA can sometimes induce manufacturers to develop the additional data that EPA considers necessary by offering to suspend the PMN process in the meantime. In negotiating with manufacturers, EPA may request tests listed in the guidelines for testing existing chemicals or additional tests. If EPA finds that the chemical may present an unreasonable risk, it can halt the use of the chemical pending development of adequate data to resolve the issue of risk. If EPA finds positive evidence that a chemical presents or will present unreasonable risks, it can ban or limit the use of the chemical.

A neurotoxicologist is present from the early stages of a PMN review for all chemicals except polymers, which, because of their low reactivity and low potential for absorption, generally present lower toxicity hazards and are thus evaluated separately. EPA has identified at least six classes of chemicals (acrylamide derivatives, acrylates, carbamates, phosphines and phosphates, pyridine derivatives, and imidazoles) that should alert reviewers to the potential for neurotoxicity during the structure-activity review. Other chemicals likely to cause concern include quaternary ammonium compounds, glycol ethers, and miscellaneous halogenated solvents. OTS is developing a more explicit set of classification criteria for neurotoxicity in order to standardize the procedures; even so, EPA neurotoxicologists have expressed concern that accurate structure-activity predictions may not be possible without information on mechanisms of action, which is available for only a few classes of chemicals (including quaternary ammonium, organophosphate compounds, and some solvents).

Neurotoxicity concerns are one of the triggers for placing a chemical into the standard review process. However, most chemicals identified as being potentially neurotoxic do not enter that process, for a variety of reasons, including lack of adequate data to support a case, lack of a strong structure-activity relationship, data indicating that human exposure would be minimal (or inadequate data on exposure), or lack of appreciation by individuals analyzing the data of certain neurobehavioral effects.

Some 220 of the approximately 1,200 chemicals (out of 6,120 PMNs submitted) that underwent standard review during fiscal years 1984 through 1987 were identified as being potentially neurotoxic. However, neurotoxicity was not the basis for most regulatory actions taken by EPA. EPA was not able to provide precise information on the extent to which concerns about neurotoxicity did influence regulatory decisionmaking, although such an analysis is now pending (5,24).

Regulation of Existing Chemicals

Existing chemicals are regulated under several sections of TSCA. Section 4 allows EPA to rule that

Box 7-D-Confidential Business Information Under TSCA: Does It Influence Regulatory Effectiveness?

In order to assess accurately the toxic risks posed by a chemical, a considerable amount of information must be reviewed, including the identity, properties, and intended uses of the chemical. Depending on the particular chemical and its application, some of this information may represent trade secrets that, if known to a competitor, would place the manufacturer or importer of a chemical at a competitive disadvantage.

The approach taken under the Toxic Substances Control Act (TSCA) toward the protection of trade secrets has been to allow nearly all information submitted to the Environmental Protection Agency (EPA) on a premanufacture notice (PMN) for a chemical to be claimed as confidential business information (CBI). Information covered by such a claim is divulged only to EPA employees who have been granted a special CBI clearance, primarily selected staff from and contractors for the Office of Toxic Substances (OTS). CBI may be released only if the Administrator determines that it is necessary to do so to protect against an unreasonable risk, and submitters must be given 30 days' advance notice of CBI releases. EPA officials or officials of other Federal agencies may obtain access to needed CBI materials, but given the breadth of information covered by CBI claims, these officials are not in a position to know what CBI information in OTS files is relevant to the performance of their duties.

The protection of CBI offered by TSCA is considerably greater than that offered by the confidentiality provisions of some other laws. For example, under Title III of the Superfund Amendments and Reauthorization Act, only the specific identity of a chemical covered by the reporting provisions of the Act can be claimed to be confidential. Further, under TSCA, the burden of challenging CBI claims falls on EPA; PMN submitters are not required to substantiate CBI claims unless challenged.

Toxicity data per se cannot be claimed as CBI under TSCA, but much of the other information relevant to assessing toxic risks can be—including the identity of the chemical for which toxicity data are presented, its physical-chemical properties, and its intended uses. These provisions of TSCA present significant obstacles to effective regulation, not only with respect to the PMN program, but also with respect to other regulatory programs, both inside and outside EPA. Three general types of obstacles can be identified: added administrative burdens on OTS, interference with effective cooperation among regulatory programs, and prevention of public oversight of the regulatory process.

Within the PMN program, CBI requirements have required OTS not only to maintain duplicate sets of records (CBI and non-CBI), but also duplicate computer databases and even duplicate computers. Public interest groups and other interested members of the public have no access to information that would allow them to questioner to accept—EPA's actions on PMNs, Neither can members of the public take any action for self-protection, as they are frequently kept from information regarding the identity of toxic chemicals or the products that might contain them. TSCA CBI provisions also pose a serious obstacle to the involvement of regulatory, academic, and industrial scientists who could assist OTS in assessing the risks of PMN chemicals.

Because CBI has the capability to "contaminate" information systems (any document or information system that contains CBI becomes CBI itself), the impediments to regulatory effectiveness posed by CBI have spread from the PMN program to programs dealing with other aspects of TSCA. Rule-making on asbestos is a particularly egregious example, where much of EPA's supporting analysis could not be made available for public review because it was based on CBI.

Persons involved in other regulatory programs, whether inside or outside of government, are not in a position to obtain information that could make important differences in the implementation of regulations. A Resource Conservation and Recovery Act permit writer in an EPA regional office, for example, will not have access to information that might significantly influence decisions regarding the disposal of TSCA chemicals; and the Consumer Product Safety Commission may not be made aware of information regarding chemicals in consumer products.

Few persons would dispute the principle of protecting true trade secrets. There is good reason, however, to question whether the burden imposed by the liberal confidentiality provisions of TSCA on the government, the public, and even industry is justifiable. Industry has managed to adapt to the less protective provisions of other laws, and alternative strategies for protecting proprietary information (e.g., patents) are available.

SOURCE: Office of Technology Assessment, 1990.

chemicals or mixtures be tested for health and environmental effects if the Agency determines that:

> (A)(i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment (ii) there are insufficient data and experience on which the effects of. . . such activities on health or the environment can reasonably be predicted, and (iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or (B)(i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture [sec. 4 (a)(l)].

If EPA can show that there is inadequate information on the effects of a compound *and* that testing is necessary to obtain such information, it is required to write a test rule that defines what is to be tested and what particular tests are to be performed. OTS has developed guidelines that describe the general procedures for the conduct of toxicity tests (40 CFR 796), although each test rule contains specific requirements for the individual chemical involved.

In contrast to FIFRA, TSCA has mandated an explicit means of identifying chemicals that must be tested by EPA for their effects on health and the environment-namely, the Interagency Testing Committee (ITC). The ITC is a multidisciplinary advisory panel composed of one member each from EPA, the Occupational Safety and Health Administration, the Council on Environmental Quality, the National Institute for Occupational Safety and Health, the National Institute of Environmental Health Sciences, the National Cancer Institute, the National Science Foundation, and the Department of Commerce. ITC conducts an ongoing, independent review of chemicals in commerce, based on recommendations from members as well as external nominations, in order to select chemicals for testing. (ITC reviews data from the published literature and solicits information from the public and from manufacturers.) The committee recommends testing priorities based on the finding that there are insufficient data to assess the hazards posed by a substance or the finding that potential human exposures are significant. (ITC has no overarching responsibility to coordinate agency testing; it simply suggests high-priority chemicals for EPA to investigate.)

ITC publishes its findings in the Federal Register and submits to EPA all data located on the substance, as well as important gaps in data, by means of a priority list which is updated every 6 months. The committee may indicate particular effects for which it believes that a substance should be tested, or it may simply point to high exposure and a general lack of data as justification for including a chemical on the priority list.

Chemicals selected for review and testing are subjected to an extensive evaluation by ITC members, experts called onto review documents, and any persons who nominate chemicals for review. EPA then conducts its internal review, which involves a multidisciplinary team, including neurotoxicologists if indicated. The group may also request assistance from EPA research personnel.

EPA examines the concerns raised by ITC and decides whether or not to issue a test rule for a substance. EPA is not limited to the issues raised by ITC; it may decide that some concerns are unjustified, or it may identify additional issues that were not mentioned in ITC's recommendations. The main reasons for which EPA may decide not to test a chemical are the determination that adequate data for a risk decision *are* available or that the chemical is no longer used in commerce. In three cases, EPA has issued test rules on chemicals that were not nominated by the ITC. If EPA decides to pursue testing, it may require tests on the basis of hazard concerns raised in the review or a high volume of production. EPA has developed guidelines for the types of tests that may be required; these are published in the Code of Federal Regulations (40 CFR 795; 40 CFR 798).

EPA can seek additional data under section 4 of TSCA by negotiating a consent decree, which is a legally binding mutual agreement that industry will conduct specified tests and that EPA will not make additional requests. The process of negotiating a consent decree can be faster and more efficient than formal rule-making, and EPA generally prefers this option. In either case, the manufacturer must conduct additional tests and submit the data to EPA in a timely manner. Once the test data have been developed and submitted, section 6 of TSCA authorizes EPA to restrict or prohibit the production, use, and disposal of the substance if the data indicate an unreasonable risk.

Box 7-E—Regulating for Neurotoxicity v. Other Toxic Effects: The Case of Acrylamide

One of the first chemicals that the Interagency Testing Committee (ITC) considered, shortly after it began operations in 1977, was acrylamide, a chemical with a variety of commercial uses. Acrylamide was already known to cause severe neurotoxic effects, but its ability to cause other chronic effects had not been well characterized. ITC noted this state of research and recommended that acrylamide be tested for effects other than neurotoxicity. The Environmental Protection Agency (EPA) had to decide whether the known neurotoxicity of this chemical was sufficient for regulatory purposes or whether additional data documenting its effects on health were necessary.

In its response to the ITC, EPA chose not to require testing of acrylamide, for two reasons. First, EPA believed that acrylamide was so neurotoxic that regulatory restrictions would be imposed to the maximum degree possible on the basis of known effects, and additional test information would be of little regulatory significance. Second, EPA noted that a chemical company was already in the midst of performing a long-term bioassay for other effects, so if additional data were, in fact, necessary, they were already forthcoming.

When the chemical company in question learned that EPA was not going to require testing, it decided to suspend its test for toxic effects other than neurotoxicity. EPA then had to decide whether neurotoxicity would be considered the driving effect or whether to impose new testing requirements. EPA retreated from its earlier position that the neurotoxicity data were sufficient and decided that data on other effects were needed. As a result, EPA persuaded the company to resume its testing and withheld assessments and final regulatory decisions pending those additional data.

SOURCE: W.R. Muir, former director, Office of Toxic Substances, U.S. Environmental Protection Agency, and President, Hampshire Research Associates, personal communication, 1988.

Neurotoxicity is one of the specific concerns that may be identified by ITC in recommending that a substance be tested, in which case EPA must respond either by including a requirement for neurotoxicity testing in its test rule or by justifying the exclusion of neurotoxicity tests. In the 24 ITC reports to the EPA Administrator issued between October 1977 and May 1989, the ITC proposed 100 chemicals or chemical classes[7] for inclusion in the TSCA section 4 priority list for testing. Of these proposals, one-third included an expression of concern regarding possible neurotoxicity (box 7-E).

Current EPA policy is to specify neurotoxicity testing both when a chemical "may present an unreasonable risk" of neurotoxicity and when there may be substantial human exposure. Under an 'A' finding (an unreasonable risk finding), a core test battery for neurotoxicity is recommended; the core battery includes a functional observational battery (FOB), motor activity tests, and neuropathological evaluations. When appropriate, these tests can be combined with other toxicity studies. Unless otherwise specified, it is assumed that both acute and subchronic testing will be conducted using the FOB and motor activity protocols, with neuropathological tests following subchronic exposures.

It may be necessary to examine other endpoints for specific chemicals, depending on their structure or the nature of existing data. Among the additional tests specified in EPA guidelines are schedule-controlled operant behavior (SCOB), developmental neurotoxicity, peripheral nerve function, and neurotoxic esterase (NTE). For organophosphates and related compounds, study design would include a 28-day repeated exposure period (e.g., 5 days per week) and NTE, ataxia, and neuropathological tests.

Because of the wide variety of production levels and exposure patterns among chemicals, EPA has developed a three-level approach to testing under a "B" finding (significant quantity finding). Testing of level 1 chemicals (low production, low exposure) generally includes the three core tests. FOB and neuropathology are considered a minimum requirement, although a 28-day subchronic study may be used in place of the usual 90-day study. For organophosphorous compounds, acute NTE and acute delayed hen tests are required. For level 2 chemicals (medium production and exposure, consumer exposure), the core battery is required; when appropriate, these tests may be combined with other toxicity studies. Level 3 chemicals (high production, high exposure) also require the core battery, and

[7]The actual number depends on the breadth of the *class* designation used.

Table 7-2-Chemicals Subject to Neurotoxicity Evaluation Under Section 4 of TSCA

Chemical	Current status	Neurotoxicity test; notes
Aniline and substituted anilines	Enforceable consent agreement announced 8/88 (53 FR 31 804)	Not being pursued for neurotoxicity; originally proposed on basis of ability to induce anoxia
Aryl phosphates	Advanced notice of proposed rule-making 12/83 (48 FR 57452)	Proposed rule under development
Cresols	Notice of final rule-making 5/87 (52 FR 19082)	FOB, MA, and NP (subchronic) added to ongoing studies by Office of Drinking Water
Cumene	Final rule 7/88 (53 FR 28195)	FOB, MA, NP (subschronic)
Cyclohexane'	Proposed rule 5/87 (52 FR 19096)	FOB, MA, NP, (subchronic); SCOB (subchronic and acute); DN if warranted after other studies completed
Cyclohexanone*	Negotiated testing agreement 1/84 (49 FR 136)	DN
1,2-Dichloropropane	Final rule 9/86 (51 FR 32079); test standard 10/87 (52 FR 37138)	FOB, MA, NP (subchronic)
Diethylene glycol butyl ether (and corresponding acetate)	Final rule 2/88 (53 FR 5932)	FOB, MA, NP (subchronic)
Diisodecyl phenyl phosphite (PDDP)	Consent order, 2/89 (54 FR 81 12)	NTE, delayed neurotoxicity (subchronic)
Ethyltoluenes, trimethylbenzenes, and C9 aromatic fraction	Final rule 5/85 (50 FR 20662); test standard 1/87 (52 FR 2522)	FOB, MA, NP (subchronic)
Commercial hexane	Final rule 2/88 (53 FR 3382)	SCOB (acute), FOB (subchronic), MA, NP
Hydroquinone and quinone	Final rule 12/85 (50 FR 53145); 5/87 (52 FR 19865)	FOB, NP (subchronic); existing data on motor activity
Isopropanol	Proposed rule 3/88 (53 FR 8638)	FOB, MA, (acute); FOB, MA, NP (subchronic); DN
2-Mercaptobenzothiazole	Final rule 9/88 (53 FR 34514)	FOB, MA, NP (subchronic)
Methyl ethyl ketoxime	Proposed rule 9/88 (53 FR 35838)	FOB, MA (acute and subchronic); NP (subchronic)
Methyl-tert-butyl ether (MTBE)	Consent order 3/88 (53 FR 10391)	FOB, MA, (acute and subchronic); NP (subchronic) testing begun
Oleylamine	Final rule 8/87 (52 FR 31962)	No neurotoxicity testing in final rule, although was in proposed rule
Unsubstituted phenylenediamines (o,m,p)	Extension of comment period 1/88 (53 FR 913)	Revised notice includes FOB, MA (acute, all three isomers, subchronic triggered from acute)
Tributyl phosphate	Proposed rule 11/87 (52 FR 43346)	FOB, MA (acute and subchronic);NP (subchronic)
1,1,1 -Trichloroethane	Consent order in preparation 8/87 (52 FR 31445)	FOB, electrophysiology (acute and subchronic)
Triethylene glycol ethers	Consent order 4/89 (54 FR 13470); final rule for DN (54 FR 13473)	FOB, MA (acute and subchronic); NP (subchronic); DN
Urea-formaldehyde resins	Advanced notice of proposed rule-making	No rule issued

KEY:
DN-developmental neurotoxicity tests
FOB-functional observational battery
MA-motor activity test
NP-directed neuropathological studies
NTE-neurotoxic esterase
SCOB-schedule-controlled operant behavior
Rule-making began prior to issuance of neurotoxicity test guidelines.

SOURCE: Office of Technology Assessment, 1990.

developmental neurotoxicity tests may be required in the near future. EPA neurotoxicologists may add tests to any of the above requirements if existing data indicate the need.

To date, test rules or consent decrees for 19 chemicals or chemical classes have included neurotoxicity testing (table 7-2). In four cases, a test protocol for developmental neurotoxicity was also considered, either as a definite requirement or in the event that other tests indicated neurotoxic effects in adults.

In the event that testing conducted under TSCA section 4 indicates that a chemical poses an unreasonable risk, section 6 gives EPA the authority to regulate production, distribution, use, or disposal of chemicals in commerce, if there is "a reasonable basis' to conclude that any of these activities "presents or will present an unreasonable risk of

injury to health or the environment" [sec. 6(a)]. In order to take a regulatory action, the burden of proof again falls on EPA to show that the listed activities "will present" a risk. EPA may then promulgate rules "to the extent necessary to protect adequately against such risk using the least burdensome requirements" [sec. 6(a)]. This provision has been used for the regulation of a very limited number of chemicals, among them PCBs, dioxin, and, most recently, asbestos.

Finally, TSCA authorizes EPA to require that new information regarding harmful effects of chemical substances be reported:

> . . . any person who manufactures, [imports,] processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the [EPA] Administrator of such information . . . [sec. 8(e)].

STANDARD-SETTING LEGISLATION AND REGULATIONS

These statutes authorize regulatory agencies to set standards for chemicals in specific situations or environments. Emissions from smokestacks, automobile exhaust, and sewage pipes, as well as chemicals found in the workplace and in consumer products, are subject to restrictions mandated by various standard-setting statutes. Some of the major standard-setting statutes—the Clean Air Act, the Federal Water Pollution Control Act as amended by the Clean Water Act, and the Safe Drinking Water Act-are pollution control measures. Others focus on the safety, labeling, and packaging of consumer and household products, including the Consumer Product Safety Act, the Federal Hazardous Substances Act, and the Poison Prevention Packaging Act. A third type of standard-setting statute, characterized by the Federal Mine Safety and Health Act and the Occupational Safety and Health Act, addresses issues of workplace safety. (See table 7-1 for key features of these statutes.)

In contrast to the regulatory activity mandated by licensing statutes, regulatory programs charged with setting standards cannot require that chemical substances be tested for toxicity. For the most part, standard-setting programs must base their decisions on reviews of existing literature on toxicology,

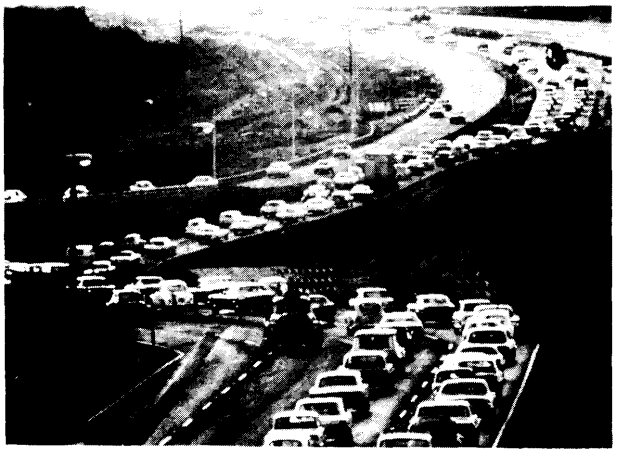

Photo credit: National Archives

although some of them have limited research capabilities as well (see ch. 4). Once a standard is set, the primary regulatory activity is enforcement—making sure that standards are not exceeded.

Clean Air Act

The Clean Air Act (CAA) (Public Law 159) was passed in 1955 "to provide research and technical assistance relating to air pollution control. The Act cited "dangers to the public health and welfare" as an adverse effect of concern. The 1970 amendments (Public Law 91-604) defined more specific effects and authorized an accelerated research program:

> . . . to improve knowledge of the contribution of air pollutants to the occurrence of adverse effects on health, including, but not limited to, *behavioral,* physiological, toxicological, and biochemical effects . . . and the short- and long-term effects of air pollutants on welfare [sec. 2(f) (l)] [emphasis added].

The 1970 amendments also called for EPA to set standards limiting hazardous air pollutants based on their effects on the public health and welfare. Recent amendments have refined the standard-setting procedures further and have revised the schedule for meeting standards. The air pollution control framework set forth by the Clean Air Act calls for EPA to establish standards for ambient air, emissions of hazardous substances, and emissions from automobiles, including fuel and fuel additives.

EPA regulates air pollutants by setting National Primary and Secondary Ambient Air Quality Standards as necessary to protect public health, with 'an adequate margin of safety" [sec. lo]. EPA

has interpreted the requirement for "an adequate margin of safety' as intending:

> . . . to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It is also intended to provide a reasonable degree of protection against hazards that research has not yet identified (50 FR 37484).

The primary standard is to be based solely on health concerns (50 FR 37484). However, a regulatory impact analysis is conducted to obtain information and provide a cost-benefit analysis for various alternative standards (22).

The Act defines a hazardous air pollutant as:

> . . . an air pollutant to which no ambient air quality standard is applicable and which in the judgment of the Administrator causes, or contributes to, air pollution which may reasonably be anticipated to result in an increase in mortality or an increase in serious irreversible, or incapacitating reversible illness [sec. 1 12(a)(l)].

It directs EPA to set emissions standards for such pollutants at a level that will provide "an ample margin of safety to protect the public health" [sec. 1 lo]. In its promulgation of National Emissions Standards for Hazardous Air Pollutants, EPA has interpreted "ample margin of safety" as not requiring the total elimination of risk (40 CFR 19 ed. 61).

The Act specifically prescribes that EPA set standards for vehicle emissions, fuel, and fuel additives. A fuel or fuel additive may be regulated only on the basis of endangerment of the public health or welfare and then only". . . after consideration of all relevant medical and scientific evidence . . . including consideration of other technologically or economically feasible means of achieving emission standards . . ." [WC. 21 l(c)(2)(A)].

EPA has promulgated Primary National Ambient Air Quality Standards for the following six pollutants: sulfur oxides, particulate matter, carbon monoxide, ozone, nitrogen dioxide, and lead (40 CFR 50). Standards for carbon monoxide (36 FR 8186) and lead (43 FR 46254) were set in response to neurotoxic effects caused by these compounds.

The original carbon monoxide standards were based on evidence that the ability to discriminate time intervals was impaired in humans when 2 to 3 percent of the body's hemoglobin—the oxygen-binding component of red blood cells—was bound to carbon monoxide (forming carboxyhemoglobin, COHb) and was therefore unable to bind to and carry oxygen (28). The impairment of time discrimination, a neurotoxic effect, was considered the most sensitive effect. The study from which these data were derived, however, has been discredited (45 FR 55066). On August 18, 1980, after reviewing the literature, including that published since the original standards were promulgated, EPA proposed retention of the 8-hour primary standard [9 parts of carbon monoxide per million parts of air (ppm)] and revision of the l-hour standard (from 35 ppm to 25 ppm), based on cardiotoxic rather than neurotoxic effects (45 FR 55066). In order to set an ambient air standard, the Agency used an equation to estimate the concentrations of carbon monoxide in ambient air that were likely to result in COHb levels of concern (45 FR 5506).

Since that time, an expert committee convened by EPA has determined that EPA should not rely on these data (50 FR 37484). After further review of the scientific literature, however, EPA decided to let stand the current primary carbon monoxide standards, which are based on concern for central nervous system and cardiovascular effects, the latter being considered to be the more sensitive (50 FR 37484). Effects on the central nervous system of low levels of COHb include "impairment of vigilance, visual perception, manual dexterity, learning ability, and performance of complex tasks" (50 FR 37484). The population most sensitive to the cardiovascular effects included persons with angina and other cardiovascular diseases. The standard was set at a level which was estimated to keep more than 99.9 percent of this sensitive population below 2.1 percent COHb (50 FR 37484).

The primary lead standard was based on impaired heme synthesis (heme is a nonprotein iron compound that gives hemoglobin its characteristic color and oxygen-carrying properties) and nervous system deficits, which included cognitive deficits, encephalopathy, and peripheral neuropathy (43 FR 46254). Children were considered to be the most sensitive population, and the standard was set at a level estimated to keep 99.5 percent of children below what was considered to be the maximum safe level of 30 micrograms of lead per deciliter of blood (43 FR 46254). The actual standard was calculated based on 20 percent of lead in the blood being

contributed from the air and 80 percent from other sources.[8] The lead standard is presently under review by EPA, and nervous system disturbances are still one of the most sensitive categories of effects (9).

National Emission Standards for Hazardous Air Pollutants have been promulgated by EPA for the following: benzene arsenic, beryllium, mercury, vinyl chloride, asbestos, and radionuclides. Only the standard for mercury was based on concerns about neurotoxic effects (38 FR 8820). The endpoint that was the driving force behind this standard was paresthesia (tingling, burning sensations) (45).

Automobile and other vehicle emissions are regulated by the Office of Mobile Sources. To date, carbon monoxide, nitrogen oxides, hydrocarbons, and particulate have been regulated. Of these four pollutants, carbon monoxide was regulated in part on the basis of neurotoxic concerns, the same concerns on which the Primary National Ambient Air Quality Standard for carbon monoxide was based. The standard itself varies, depending on the vehicle class and model year.

EPA regulates the lead content of gasoline on the basis of the same neurotoxic effects cited in the primary national ambient air quality standard for lead (50 FR 9386). A standard of 0.1 gram of lead per gallon of leaded gasoline became effective January 1, 1986. EPA was particularly concerned about the impact of lead on the health of preschool children and has clearly stated that its long-term objective is to eliminate the use of lead in gasoline (50 FR 9386).

Proposed Amendments

Efforts to amend the CAA during the IOOth Congress were not successful. More than 30 different bills proposing amendments to CAA, including an Administration proposal, have been introduced in the House and Senate during the 10lst Congress, and hearings have been held on many of them. Although the issue is being actively debated and the CAA will almost certainly be amended, it is too early to tell what form the amendments will take and what direct effect, if any, the amendments will have on the regulation of neurotoxic substances.

Federal Water Pollution Control Act and Clean Waler Act

The Federal Water Pollution Control Act (FWPCA) (33 U.S.C. 466) and amendments to it, including the Clean Water Act (CWA), established a framework for the control of water pollution based on human health and environmental concerns. The 1972 amendments (Public Law 92-500), which completely revised earlier versions of FWPCA, authorized EPA to set effluent standards for a designated list of hazardous substances (40 CFR 116). Further amendments to the FWPCA, including the 1977 Clean Water Act, authorized EPA to develop and periodically review water quality criteria that accurately reflect ''the latest scientific knowledge" on "the kind and extent of *all identifiable effects on health and welfare' [sec.* 304(a)(l)] [emphasis added]. The criteria are not regulations and, as such, carry no enforcement authority. However, they provide guidance for the derivation of regulatory standards, including general effluent limitations and toxic pollutant effluent limitations authorized by the FWPCA (45 FR 79319).

EPA is authorized to establish water quality criteria to protect human health and the environment. The criteria to protect human health are "based solely on data and scientific judgments on the relationship between pollutant concentrations and environmental and human health effects. . . and do not reflect considerations of economic or technological feasibility" (45 FR 79319).

EPA's Office of Water Regulations and Standards has established three types of water quality criteria for pollutants where sufficient data are available: 1) to protect freshwater aquatic life, 2) to protect saltwater aquatic life, and 3) to protect human health. Derivation of criteria to protect human health was based on three endpoints: carcinogenicity, adverse noncarcinogenic effects, and organoleptic effects (45 FR 79347). (Organoleptic effects refer to taste or odor characteristics of a compound and have no demonstrated adverse effects on human health.) Criteria were based on organoleptic effects when the organoleptic threshold was lower than that calcu-

[8]The Lead Industries Association, Inc., challenged the standard in court, arguing that EPA could only regulate based on "clearly adverse effects'' and that the nervous system effects had not been adequately documented at the levels cited by EPA (17). The court upheld EPA's standard, however, noting that the EPA Administrator's actions were reasonable, that EPA did, in fact, have sufficient evidence suggesting nervous system effects, that the statute allows the EPA Administrator considerable discretion to determine adverse effects, and that in any event the standard was based in part on providing an "adequate margin of safety,' which is required by the Clean Air Act.

lated from toxicity data or when there were insufficient toxicity data.

Water quality standards set to protect human health and based on toxicological data have been established for 86 compounds (45 FR 7931 8; 49 FR 5831). For four of these, lead, mercury, thallium, and toluene, neurotoxic effects were of major concern (34-44). A brief survey of the water quality criteria documents (34-44) indicates that at least eight other chemicals are noted as causing neurotoxic effects, even though the standards for these chemicals were based on other endpoints (9).

Safe Drinking Water Act

The Safe Drinking Water Act (SDWA) of 1974 amended the Public Health Service Act ''to assure that the public is provided with safe drinking water" (Public Law 93-523). SDWA and its amendments instituted a framework of primary and secondary water regulations designed to control contaminants in public drinking water supplies that EPA determines 'may have any adverse effect on the health of persons" [sec. 1401(1)(B)].

Under the Act, EPA was to establish Revised National Primary Drinking Water Regulations, using a two-stage process. First, EPA was to establish recommended maximum contaminant levels (RMCLs), which are nonenforceable health goals. RMCLs were to be set "at a level [at] which. . . no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety" [sec. 1412(b)(l)(B)]. For carcinogenic pollutants, the RMCL was to be set at zero. Once an RMCL had been promulgated, EPA was to establish a maximum contaminant level (MCL) for that pollutant. An MCL was an enforceable standard and is to be set:

> . . . as close to the recommended maximum contaminant levels. . . as is feasible. . . [i.e.], with the use of the best technology, treatment techniques, and other means, which the Administrator finds are generally available taking costs into consideration [sec. 1412 (b)(3)].

A treatment technique maybe established instead of an MCL if "it is not economically or technologically feasible to . . . ascertain the level of . . . [a] contaminant [in drinking water]" [sec. 1401 (C)(ii)].

When the Act was amended in 1986, the two-step process was retained, with EPA to specify nonenforceable goals [RMCLs were renamed maximum contaminant level goals (MCLGs)], on which MCLS were to be based. EPA was required to propose and promulgate MCLGs and MCLs simultaneously for any chemical. Another key feature of the amendments, from a neurotoxicological perspective, was the imposition of a ban on the use of lead pipe, solder, or flux in plumbing for drinking water after June 19, 1986.

The Office of Drinking Water of EPA has set MCLGs for carcinogenic pollutants at zero. MCLGs for noncarcinogenic agents are set by establishing the dose at which harmful effects may be observed and then compensating for uncertainties in the process (50 FR 46946). EPA then predicts exposures from food and air sources and sets the MCLGs accordingly (50 FR 46946).

Since the revision of the Act, MCLGs have been set for fewer than 15 inorganic chemicals under the National Primary Drinking Water Regulations (48 FR 45502). Of the 10 MCLs issued, three were based partly or entirely on nervous system effects: 1) barium, 2) lead, and 3) mercury. For one, arsenic, the nervous system was mentioned as one of several organ systems affected with more severe intoxication, but the MCL was not based on this (33).

The National Primary Drinking Water Regulations also contain MCLs for 10 organic chemicals: four pesticides, two herbicides, and four trihalomethanes. It is difficult to ascertain the effects of concern for the four pesticide and two herbicide MCLs. According to one EPA document, the severity of the symptoms of the pesticides (endrin, lindane, methoxychlor, and toxaphene) is related to the concentrations of the compounds in the nervous system (33). Specific effects of concern for the two herbicides [2,4-D and 2,4,5-TP (Silvex)] are not mentioned (33). The standard for the four trihalomethanes was based on chronic low-level effects (primarily cancer), although these compounds do have an acute effect on the nervous system.

In addition to setting drinking water standards, the Office of Drinking Water publishes health advisories describing levels of contaminants. These advisories cover l-day, 10-day, long-term (approximately 7 years, or 10 percent of an individual's lifetime), and lifetime exposures. The advisories are not federally enforceable but describe levels of contaminants in drinking water that are associated with adverse health effects. The advisories do not

clearly indicate the effects that are of primary concern, but one or more of the advisories for seven contaminants appear to have been based on neurotoxic effects (50 FR 46936).

Consumer Product Safety Act and Federal Hazardous Substances Act

The Consumer Product Safety Act (Public Law 92-573) of 1972 established the Consumer Product Safety Commission (CPSC) as an independent regulatory commission charged with protecting the public from "unreasonable risks of injury associated with consumer products" [sec. 2(a)(3)]. Risk of injury is defined as "risk of death, personal injury, or serious or frequent illness" [sec. 3(a)(3)].

The Act authorizes CPSC to promulgate consumer product safety standards, including performance requirements and warning or instructional labels, necessary to 'prevent or reduce an unreasonable risk of injury associated with such product" [sec. 7(a)]. The determination of whether or not a particular risk of injury is unreasonable involves balancing ". . . the probability that the risk will result in harm and the gravity of the harm against a rule's effects on the product's utility, cost, and availability to the consumer" (42 FR 44198). The Consumer Product Safety Act's broad authority could cover products with neurotoxic effects, but toxic substances in general are more likely to be regulated under the Federal Hazardous Substances Act because the former prohibits the regulation of a risk that can be adequately regulated under the latter [sec. 30(d)].

The Federal Hazardous Substances Act (Public Law 86-613) was passed in 1960 to protect the public health by requiring that hazardous substances be labeled with various warnings, according to the nature of the hazard. The Act defines a ''hazardous substance' as:

> *Any* substance or mixture of substances which (i) is toxic, (ii) is corrosive, (iii) is an irritant. . . if such substance or mixture of substances *may cause substantial personal injury or substantial illness* during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children [sec. 2(f)(l)] [emphasis added].

A toxic substance is defined as "any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface" [sec. 2(g)].

The Act directs CPSC to issue regulations clarifying which categories of substances fit the various definitions of hazardous, if there is any uncertainty [sec. 3(a)(l)], and to ban substances through a formal rule-making procedure:

> . . . on the basis of the finding that, notwithstanding such cautionary labeling as is or may be required under this Act for that substance, the degree or nature of the hazard involved in the presence or use of such substance in households is such that the objective of the public health and safety can be adequately served only by keeping such substance . . . out of the channels of interstate commerce . . . [sec. 2(q)(l)].

The Act calls for banning substances that are too dangerous for household use.

Because of the interrelatedness of concerns embodied in the Consumer Product Safety Act and the Federal Hazardous Substances Act and because both are administered by CPSC, regulatory actions under the two statutes have been closely intertwined. CPSC has responded to its mandate by setting standards for various consumer products. Its actions based on neurotoxicity concerns have been to ban products with paint or other surface material containing lead in excess of 0.06 percent (42 FR 44199). This standard was designed "to reduce or eliminate the unreasonable risk of injury associated with lead poisoning in children' (42 FR 44198) and addressed consumer products that bear lead-containing paint, including toys and other items used by children and furniture used by consumers (42 FR 44199). The Commission cited the following as adverse effects of lead on the nervous system: hyperactivity, slowed learning ability, withdrawal, and blindness (42 FR 44200).

CPSC has been involved in working out a voluntary consensus on the labeling of various consumer products containing organic solvents such as n-hexane. Concern about these compounds was based on the association between repeated exposure to solvents and permanent neurological damage. CPSC recently hired a staff neurotoxicologist but has not undertaken any specific neurotoxicity product evaluations lately. The Commission does, however, plan to draft criteria for classifying, evaluating, and labeling products that warrant concern for neurotoxic effects (under the authority of both Acts).

Federal Mine Safety and Health Act

The Federal Mine Health and Safety Act of 1969 (Public Law 91-173), as amended in 1977 (Public Law 95-173), grew out of congressional concern over the:

> . . . urgent need to provide more effective means and measures for improving the working conditions and practices in the Nation's coal or other mines in order to prevent *death and serious physical harm,* and in order to prevent *occupational diseases* originating in such mines [sec. 2(a)] [emphasis added].

Although no specific toxic effects are singled out for consideration, the concern about physical harm and occupational diseases could encompass neurotoxic effects.

The Act established the Mine Safety and Health Administration (MSHA) in the Department of Labor and authorized it to "develop, promulgate, and revise, as may be appropriate, improved mandatory health or safety standards for *the protection of life and prevention of injuries* in coal or other mines' [sec. 10l(a)] [emphasis added]. MSHA is to ensure that miners will not ''suffer material impairment of health or functional capacity even if such miner has regular exposure to the hazards dealt with by such standard for the period of his working life" [sec. l o] .

MSHA initially fulfilled its standard-setting mandate by adopting standards for airborne contaminants recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) (box 7-F), and the American National Standards Institute (30 CFR 57.5). In 1981, MSHA began a comprehensive review of its safety standards, including those for air (46 FR 57253,46 FR 10190); since then, it has moved to update its regulations by incorporating more recent threshold limit values (see ch. 6).

Occupational Safety and Health Act

The Occupational Safety and Health Act (OSH Act) was enacted in 1970 to improve workplace safety. The Act established the Occupational Safety and Health Administration (OSHA) in the Department of Labor and directed it to promulgate health and safety standards, defined in the Act as:

> . . . conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe or healthful employment and places of employment [sec. 3(8)].

The Act also authorizes OSHA to promulgate new standards for toxic materials and to modify or revoke existing ones, to ensure ". . . that no employee will suffer *material impairment of health or fictional capacity* even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life" [sec. 6(b)(5)] [emphasis added].

In 1971, OSHA adopted existing Federal standards, most of which had been adopted under the Walsh-Healy Act, and approximately 20 consensus standards of the American National Standards Institute as permissible exposure limits (PELs) (39 FR 23540).

In addition to initiating a standard-setting framework, the OSH Act established the National Institute for Occupational Safety and Health (NIOSH) as a research agency "authorized to develop and establish recommended occupational safety and health standards" [sec. 22(c)(l)] and to set criteria for such standards. Although the Act directed that the standards and criteria be used by OSHA in the promulgation of new or revised health and safety standards, OSHA has acted on few of NIOSH's recommendations. NIOSH is also responsible for assessing work-related diseases and injuries, including those caused by toxic substances.

Since the adoption of initial standards, OSHA has issued complete health standards for 25 substances (27). Of these, the one concerning lead was based, in part, on nervous system effects (43 FR 52952). Four other compounds, inorganic arsenic, acrylonitrile, ethylene oxide, and 1,2-dibromo-3-chloropropane, were cited as causing various disturbances in the nervous system, but the standards for these were driven by concerns about carcinogenic effects (29 FR 1910).

OSHA recently published a far-reaching revision and update of existing standards (54 FR 2332). The rule affects standards for 428 chemical substances: it lowers PELs for 212 substances, establishes them for 164 substances that were not formerly regulated, and maintains unchanged the existing levels for 52 substances. The regulation addressed only chemicals that were covered by the most recent ACGIH recommendations and whose threshold limit values (TLVs) differed from current PELs. No new stand-

Box 7-F—The American Conference of Governmental Industrial Hygienists

The American Conference of Governmental Industrial Hygienists (ACGIH) is a professional society organized in 1938 by a group of governmental industrial hygienists. Its recommendations have played a major role in setting standards under both the Occupational Safety and Health Act and the Federal Mine Safety and Health Act. ACGIH membership consists of government or industrial hygienists involved in occupational safety and health programs who seek to establish a consensus among industrial toxicologists on the levels of chemicals that might reasonably be considered safe in the workplace.

Over the years, ACGIH has set threshold limit values (TLVs) for hundreds of occupational substances and publishes its recommendations annually. These values refer to airborne concentrations of substances that the majority of workers maybe repeatedly exposed to on a daily basis without adverse effect (ACGIH, 1985).

ACGIH sets three types of TLVs for chemical compounds: time-weighted average concentrations, which are for an 8-hour workday and a 40-hour workweek; short-term exposure limits, which are 15-minute time-weighted average exposures not be exceeded at any time; and ceiling limits, which are not to be exceeded even for an instant (ACGIH, 1985).

There are no set guidelines for the establishment of TLVs. Rather, the values are based on the TLV committee's professional judgment, after they have reviewed information from industrial experience, from experimental human and animal studies, and, when possible, from a combination of all three. The basis on which the values are established may differ from substance to substance: protection against impairment of health maybe a guiding factor for some, whereas reasonable freedom from irritation, narcosis, nuisance, or other forms of stress may form the basis for others (ACGIH, 1985).

The TLVs are not legally enforceable but are meant to be used as guidelines. The 1968 ACGIH chemical substance TLVs and the 1969 noise TLV, however, were adopted as Federal standards under the Walsh-Healy Act prior to enactment of the Occupational Safety and Health Act. In the early 1970s, these standards were adopted as permissible exposure limits by the Occupational Safety and Health Administration, as mandated by the Act (OTA, 1985).

As of 1985, ACGIH had set 605 TLVs covering a wide range of compounds (ACGIH, 1985); TLVs for 202 of these substances were set in whole or in part to protect individuals from nervous system effects ranging from drowsiness to nerve damage. (This number does not include effects such as eye, nose, and throat irritation, although these effects might be broadly construed as neurotoxic.)

OSHA recently published a revised standard that increased the protection of workers by implementing new or revised PELs for 428 toxic substances (53 FR 20960-20991). The final standard was published in January 1989. The new rule established lower exposure limits for approximately 212 substances already regulated by OSHA. PELs would be established for the first time for another 164 substances. A large number of these are established to prevent adverse effects on the nervous system. The regulation addressed only chemicals that were covered by the most recent ACGIH recommendations and whose TLVs differed from current PELs. No new standards were promulgated for chemicals for which NIOSH had specified recommended exposure levels, unless those chemicals were also on the ACGIH list.

Critics of ACGIH argue that the TLVs are essentially industry consensus standards arrived at through a limited review of available toxicological information. Nevertheless, TLVs are widely used by both industry and government officials.

SOURCES: American Conference of Governmental Industrial Hygienists, *Threshold Limit Values for Chemical Substances in the Work Environment Adopted by ACGIH for 1985-1986* (Cincinnati, OH: 1985); U.S. Congress, Office of Technology Assessment, Preventing *Illness and Injury in the Workplace, OTA-H-256* (Washington, DC: U.S. Government Printing Office, 1985).

ards were promulgated for chemicals for which NIOSH had specified recommended exposure levels, unless those chemicals were also on the ACGIH list. This issue is discussed in more detail in chapter 10.

Tables in the Federal Register notice announcing the rule listed the explicit toxicological concerns behind 410 of the standards. Of those, PELs for 20 compounds were based on the avoidance of direct neuropathic effects. An additional 19 were based on the avoidance of narcosis. A total of 79 chemicals were regulated to prevent irritation, an effect that does not necessarily imply neurotoxicity but may include some neurotoxic effects. Methanol, a chemical that adversely affects the optic nerve, was one of

the five substances listed because of ocular concerns. Finally, 26 chemicals were listed under the category of avoidance of metabolic effects. This category contained several substances that cause neurotoxic effects, including carbon monoxide and some types of cholinesterase inhibitors (cholinesterase inhibition is discussed in chs. 3 and 10).

The rule sets standards for an additional 73 chemicals on the basis of structural analogies to other compounds with known effects. Of the 73, 18 were selected because they are analogous to compounds that induce neurological effects, narcosis, or cholinesterase inhibition. PELs for 26 chemicals were based on no observed adverse effect levels (NOAELs). For six of these, the adverse effects noted in the rule were neurological.

Although the chemicals discussed above have been regulated explicitly on the basis of neurological concerns, it should be remembered that other neurotoxic chemicals may have been regulated on the basis of other undesirable effects they induce. For example, the PEL for carbon disulfide, a well-known neurotoxicant, is based on avoidance of cardiovascular effects.

In addition to specifying PELs, OSHA has issued, and subsequently expanded, a hazard communication standard (52 FR 3 1852). This requires manufacturers and importers to assess the hazards of the chemicals they produce or import, requires employers to provide information to their employees concerning hazardous chemicals (using training, labels, material safety data sheets, and access to written records), and requires distributors of hazardous chemicals to provide information to their customers (via proper labels and Material Safety Data Sheets). It should be noted that many such data sheets contain very limited information on toxic hazards.

CONTROL-ORIENTED LEGISLATION AND REGULATIONS

Hazardous chemical substances in the environment and in consumer products are the subject of control-oriented statutes such as the Comprehensive Environmental Response, Compensation, and Liability Act, the Controlled Substances Act, the Lead-Based Paint Poisoning Prevention Act, the Marine Protection, Research, and Sanctuaries Act, the Poisoning Prevention Packaging Act, and the Resource Conservation and Recovery Act. These statutes, which are founded on a recognition of the problems caused by predetermined or specified sets of hazardous chemicals, are focused on developing procedures to control existing situations (see table 7-l). Regulatory implementation under these laws consists primarily of setting allowable levels or reporting requirements and enforcing the limits that have been set.

Comprehensive Environmental Response, Compensation, and Liability Act

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), also known as Superfund, was enacted in 1980 to provide authority for EPA to clean up hazardous waste sites. CERCLA defined hazardous substances as either compounds that have already been designated under other Acts or compounds designated by EPA" which, when released into the *environment may present substantial danger to the public health or welfare or the environment" [sec.* 102(a)] [emphasis added]. In addition to identifying hazardous substances, CERCLA directs EPA to "promulgate regulations establishing that quantity of any hazardous substance the release of which shall be reported" [sec. 102(a)], essentially supplanting a similar process established under the Clean Water Act. These reportable quantities (RQs) are used to trigger the appropriate response "necessary to protect the public health or welfare or the environment" [sec. l o] .

Initially, all RQs were set at 1 pound, unless other RQs were assigned under section 311 of the Clean Water Act. As authorized under section 102 of CERCLA, EPA has adjusted RQs for approximately 440 of the 717 substances on the list (40 CFR 302; 51 FR 34534), based on "scientific and technical criteria which correlate with the possibility of hazard or harm on the release of a substance in a reportable quantity" (48 FR 23560). The criteria EPA used were aquatic toxicity, mammalian toxicity, ignitability, reactivity, chronic toxicity, and potential carcinogenicity. Of the 245 hazardous substances evaluated by EPA's Environment Criteria and Assessment Office, 64 were reviewed for chronic toxicity. Of those 64, 22 could not be ranked due to insufficient data. Of the 42 that were ranked, 5 were ranked on the basis of effects on the nervous system (11).

Photo credit: U.S. Environmental Protection Agency

The Superfund Amendments and Reauthorization Act (SARA) (Public Law 99-499) passed in 1986 called for the development of a list of 100 high-risk chemicals from the chemicals on the Superfund list for which available data were inadequate. SARA established a research program at the Agency for Toxic Substances and Disease Registry to conduct the necessary research and to develop toxicology data profiles on the 100 chemicals. Thus, although CERCLA as amended is not a testing program, it does sponsor research. The toxicological profiles being prepared under SARA provide an explicit discussion of health effects for various routes of exposure to a chemical (oral, inhalation, dermal). The specific effects considered include systemic effects, immunological effects, neurological effects, developmental effects, reproductive effects, genotoxic effects, cancer, and death.

Controlled Substances Act

Congress passed the Controlled Substances Act in 1970 as Title II of the Comprehensive Drug Abuse Prevention and Control Act (Public Law 91-513). Finding that ". . . the illegal importation, manufacture, distribution, and possession and improper use of controlled substances have a substantial and detrimental effect on the health and general welfare of the American people' [sec. 101(2)], Congress set forth a framework for restricting a defined list of substances, many of which are drugs with beneficial as well as harmful uses.

The Act established five categories, or schedules, of controlled substances based on potential for abuse, severity of possible harmful effects, likelihood of dependence, and accepted medical uses [sec. 202; 28 CFR]. The Act grants the Attorney General and the Department of Justice authority to regulate and enforce the control of scheduled substances and to add to, remove from, or amend the schedules as appropriate.

The Controlled Substances Act calls for cooperation between FDA and the Justice Department in determining which drugs should be controlled. In addition, FDA is directed to notify the Justice Department whenever "a new drug application is submitted . . . for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, [and] it appears that such drug has abuse potential" [sec. 201(f)]. Thus, the primary scientific and pharmacological investigations, including evaluations of toxicity or of effects on the central nervous system, are handled under the FDA procedures described under FFDCA.

Marine Protection, Research, and Sanctuaries Act

Finding that "unregulated dumping of material into ocean waters endangers human health, welfare, and amenities, and the marine environment" [sec. 2(a)], Congress enacted the Marine Protection, Research, and Sanctuaries Act (MPRSA) (Public Law 92-532) in 1972 to:

> . . . regulate the dumping of all types of materials into ocean waters and to prevent or strictly limit the dumping into ocean waters of any material which would *adversely affect human health, welfare, or amenities,* or the marine environment, ecological systems, or economical potentialities [sec. 2(B)] [emphasis added].

Materials are defined as:

> . . . matter of any kind or description, including, but not limited to, dredged material, solid waste, incinerator residue, garbage, sewage, sewage sludge, munitions, radiological, chemical, and biological warfare agents, radioactive materials, chemicals, biological and laboratory waste, wreck or discarded equipment

Photo credit: U.S. Environmental Protection Agency

rock, sand, excavation debris, and industrial, municipal, agricultural, and other waste [sec. 3(c)].

The Act prohibits dumping of the defined materials in U.S. territorial waters and 12 miles beyond U.S. boundaries unless the dumper obtains a permit.

MPRSA does not establish any program or requirement for ascertaining the toxic effects of materials nor any mechanism by which specific, newly identified toxic materials may be added to the list. EPA has restricted or prohibited the dumping of several categories of substances because of toxic or radioactive effects or persistence. Mercury and mercury compounds—known neurotoxicants—are among the compounds specifically restricted (40 CFR 227.6), although the regulations do not mention neurotoxic effects in particular.

. EPA's primary regulatory responsibility under MPRSA has been control of ocean dumping sites through the permitting process (40 CFR 220-31). EPA has delegated this authority to regional EPA administrators (52 FR 25009). EPA considers the impact of the proposed dumping on ''aesthetic, recreational, and economic values, " including the "[presence in the material of toxic chemical constituents released in volumes which may affect humans directly" (40 CFR 227.18). Apart from restrictions on mercury, however, there is no clear record of how or whether specific neurotoxic effects have been regulated under MPRSA.

Lead-Based Paint Poisoning Prevention Act and Poison Prevention Packaging Act

The Lead-Based Paint Poisoning Prevention Act (LBPPPA) (Public Law 91-695) is the only statute based primarily on concerns for neurotoxic effects (see ch. 10). The purpose of the Act-to eliminate lead-based paint poisoning—was to be accomplished by screening and testing children, removing lead-based paint from buildings, and banning the use of lead-based paint in Federal construction or rehabilitation of residential housing. The 1973 amendments (Public Law 93-151) defined lead-based paint as any paint which contains 0.06 percent lead. That 0.06 percentage was based on studies indicating the permissible daily intake of lead to be 300 micrograms, which the U.S. Public Health Service and the American Academy of Pediatrics

Photo credit: U.S. *Environmental Protection Agency*

Household substances that pose a risk to children are regulated under the Poison Prevention Packaging Act.

then calculated to be a limit of no more than 0.06 percent lead by weight.

The Act was amended again in 1976 by the National Consumer Health Information and Health Promotion Act, which instructed the CPSC:

> . . . to determine, by December 23, 1976, whether a level of lead in excess of 0.06 percent but not over 0.50 percent, was safe. If the Commission were unable to determine a safe level of lead in this range, paint manufactured after June 22, 1977, containing more than 0.06 percent would be considered ''lead-based paint" (42 FR 44193).

The CPSC later ruled that available data did not support the establishment of a level in this range as being safe (42 FR 44193), so the 0.06 percent level remained in effect.

The Poison Prevention Packaging Act (PPPA) (Public Law 91-601) was enacted in 1970 to prevent inadvertent poisoning of small children by hazardous household substances. Packaging of these substances was to be done in such a way as to make it "significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance therein within a reasonable time' [sec. 2(4)]. The Act authorizes the CPSC to promulgate standard-setting rules for special packaging if the Commission determines that:

> . . . the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children *from serious personal injury or serious illness resulting* from handling, using, or ingesting such substance [sec. 3(a)(l)] [emphasis added].

The Act encompasses hazardous substances as defined in the Federal Hazardous Substances Act; foods, drugs, and cosmetics as defined in the FFDCA; and fuels packaged for household use.

Because LBPPPA and PPPA are designed to control acknowledged problems, most regulatory actions undertaken by the CPSC under these two statutes are aimed at enforcement. Under LBPPPA, the Commission may conduct periodic measure-

ments to ensure that lead in paints does not exceed the mandated level. Under PPPA, the only regulatory option is for CPSC to require protective packaging of hazardous household substances that are identified or designated as toxic by other statutes or agencies; PPPA has little impact on the substantive regulation of toxic substances.

Resource Conservation and Recovery Act

The Resource Conservation and Recovery Act (RCRA) directs EPA to identify and list hazardous wastes. Generators, transporters, and facilities that treat, store, or dispose of such wastes are then subject to regulations promulgated by the Administrator as necessary *to protect human health and the environment" [sec.* 3002(a)] [emphasis added]. A hazardous waste is defined as a:

> . . . solid waste, or combination of solid wastes, which because of its quantity, concentration, or physical, chemical, or infectious characteristics may:
>
> (A) cause, or significantly contribute to, an increase in serious *irreversible, or incapacitating reversible, illness;* or
>
> *(B) pose a substantial present or potential hazard to human health* or the environment when improperly treated, stored, transported, or disposed of, or otherwise managed [sec. 1004(5)] [emphasis added].

EPA classifies a solid waste as hazardous based on ignitability, corrosivity, and reactivity, as well as on various toxicity criteria, including fatality at low doses or the capability of "causing or significantly contributing to an increase in serious irreversible, or incapacitating reversible, illness' (40 CFR 261). Toxic wastes are designated on the basis of the nature of the toxicity of the constituent, its concentration, and its persistence (40 CFR 261.1 1). The statute allows for direct measurement of waste toxicity in some cases.

EPA has adopted standards based on the chronic health limits defined under the National Primary Drinking Water Standards; consequently, the same eight chemicals that were identified for neurotoxic concerns under the SDWA are regulated under the Resource Conservation and Recovery Act.

NEW INITIATIVES IN REGULATING NEUROTOXIC SUBSTANCES

A primary issue in regulating potentially neurotoxic substances is the adequacy of the data on which evaluations are based. Representatives of Federal regulatory agencies disagree on whether or how well current toxicity tests predict neurotoxic effects of chemicals on humans. Consequently, new initiatives for regulating neurotoxic substances have emerged in agencies dissatisfied with existing approaches.

The first tangible result of attempts to improve regulatory testing for neurotoxic effects was the publication in 1985 of a set of neurotoxicity test guidelines by EPA's Office of Toxic Substances. The primary purpose of these guidelines was to aid development of test rules under section 4 of TSCA (50 FR 39458). The significance of the guidelines is demonstrated by the fact that, since they were introduced, experimental protocols based on them have been incorporated into a substantial number of test rules and consent agreements. Studies to validate the scientific utility of the guidelines are now under way.

The two most notable ongoing regulatory initiatives concerning neurotoxicants are also centered on development of test guidelines. These initiatives, one by EPA and one by FDA, are discussed in the sections that follow. A third new initiative, which is less a change in neurotoxicity regulation than an attempt to obtain international consensus on changes already made by EPA, is an EPA proposal to the United Nations Organization for Economic Cooperation and Development (OECD) to add a mammalian neurotoxicity screening battery to OECD's test guidelines.

Revision of EPA's Neurotoxicity Test Guidelines for Pesticides

Recent efforts at EPA to coordinate evaluations of neurotoxicity under TSCA and FIFRA highlight some of the differences that have existed between the regulatory programs of the Office of Toxic Substances and those of the Office of Pesticide Programs (OPP). When OTS published its neurotoxicity guidelines in 1985, its Health and Environmental Review Division had been employing neurotoxicologists for several years, reflecting OTS's approach of having chemicals reviewed by several

scientists with different areas of toxicological expertise. In contrast, OPP's Hazard Evaluation Division has traditionally assumed equivalency of training among its toxicologists, which may have fostered some reluctance on OPP's part to focus on specific organ system tests, including neurotoxicity tests, in its evaluations. Since 1986, OPP has consulted OTS neurotoxicity test guidelines when requesting data on the neurotoxicity potential of pesticides. In that year, OPP also hired two neurotoxicologists previously employed by OTS.

Adoption of neurotoxicity testing guidelines by OPP was delayed by uncertainties regarding revision of FIFRA by Congress in late 1986, but plans to add neurotoxicity guidelines to those specified in 40 CFR 158 continued in 1987. Work on the guidelines received further impetus in February 1987, when a coalition including the Center for Science in the Public Interest (CSPI) and 11 other groups and individuals petitioned EPA to develop methods for assessing neurotoxic effects of active and inert ingredients in pesticides (10). OPP submitted its response to a subpanel of the FIFRA Science Advisory Panel (SAP) for review in October 1987, but SAP's approval of those guidelines was superseded by a decision to revise all of the part 158 guidelines, eliminating tests that are outmoded or uninformative and adding tests in several areas, including neurotoxicity and immunotoxicity.

In May 1988, the director of OPP met with representatives of CSPI and other groups who had signed the petition. In August 1988, CSPI sent a letter to EPA's administrator for pesticides and toxic substances suggesting several modifications of the revised guidelines approved by SAP. CSPI called for routine conduct of chronic neurotoxicity studies (rather than just when acute and subchronic studies indicated neurotoxic effects) and for inclusion of schedule-controlled operant behavior and developmental neurotoxicity tests on a regular basis (see ch. 5 for descriptions of these tests). CSPI also pressed for revision of the pesticide assessment guidelines (46) rather than promulgation of a regulation to add new data requirements to 40 CFR 158.

EPA responded with a letter to CSPI in November 1988, stating that the Agency intended to adhere to the guidelines recommended by the SAP subpanel and that it was still considering appropriate criteria for initiating tests beyond the base set of tests. EPA agreed to modify the pesticide test guidelines but stressed the need to coordinate OPP and OTS guideline revisions through an intra-agency work group. Draft EPA guidelines were supposed to be completed by February 1990 and made available for public comment in May 1990.

Meanwhile, efforts to improve neurotoxicity testing requirements through the 1988 amendments to FIFRA resulted in changes in the principal report accompanying these amendments. Section 219 of S. 1516 (reported by the Senate Agriculture Committee in May 1988) would have required the EPA Administrator to "develop methods for testing to accurately detect neurotoxic and behavioral effects of pesticides, and their ingredients," and "as such methods are developed, require to the extent appropriate and necessary that data from such testing be submitted by persons seeking to obtain or maintain pesticide registrations." This provision was not included in the amendments finally enacted, but the House Agriculture Committee's report on the bill that became law noted the deficiencies of EPA's current neurotoxicity testing and called for improvements:

> In light of recommendations made by a number of scientific and public health organizations urging expanded neurotoxic and behavioral testing, the Committee requests that EPA intensify the degree of such testing in its pesticide program, including testing related to chronic exposure, prenatal, and neonatal effects (26).

At present, scientists in OPP and OTS are working together to produce a set of revised neurotoxicity test guidelines (see ch. 5). The test guidelines will be accompanied by risk assessment guidelines to direct the scientific review of the data they provide (box 7-G).

Revision of the FDA's Red Book for Food and Color Additives

FDA's Center for Food Safety and Applied Nutrition has been considering the utility of specific tests for neurotoxic effects for several years. In

[9]The co-petitioners were the State of New York, the Wisconsin Public Intervener's Office, the Natural Resources Defense Council, the National Coalition Against Misuse of Pesticides, the Northwest Coalition for Alternatives to Pesticides, the American Psychological Association, the American Public Health Association, the Association of Children and Adults with Learning Disabilities, the U.S. Public Interest Research Group, and Drs. Philip J. Landrigan and Richard E. Letz, Mount Sinai School of Medicine.

Box 7-G-Flexibility in Neurotoxicological Testing

One controversy that has arisen with the introduction of neurotoxicity test guidelines by the Environmental Protection Agency (EPA) is the assertion by some scientists that test guidelines impose excessively rigid limitations on toxicological testing. These scientists, both inside and outside regulatory agencies, have stated that test guidelines result in testing that may ignore important parameters influencing a chemical's toxicity, preclude the effective use of expert scientific judgment, and stifle innovation in testing.

While acknowledging the validity of some of these objections, scientists favoring test guidelines have observed that the purpose of most toxicological testing in the regulatory context is not elucidation of mechanisms of toxicity, but rather clarification of the relative toxic hazards posed by various chemicals. (FDA's preclinical studies of drugs represent an exception to this generalization.) If toxicity test protocols are designed independently for each chemical under review, it becomes nearly impossible to compare chemicals.

Scientists with opposing views on this issue have also advanced arguments on practical grounds. Those opposed to test guidelines have stated that few contract laboratories have the capabilities to perform all of the neurotoxicological tests specified in the current EPA Office of Toxic Substances' guidelines. (However, scientists at contract testing laboratories have stated that they can implement any test procedures that are supported by an adequate market.) Opponents of test guidelines have also noted that the laboratories frequently lack an adequate set of control data to demonstrate the validity and reliability of tests. Regulatory scientists have noted that the requirements of Federal rule-making procedures would make designing new studies for each chemical of concern an extremely protracted process. (In practice, regulatory agencies have sometimes negotiated the performance of tests that differ substantially from those specified in the guidelines.)

One compromise (which has received extensive discussion but apparently little effort toward implementation) is the specification of test guidelines in terms of sensitivity. Sensitivity could be defined as the detection of effects of known toxicants (positive control studies) or as the detection of a specific decrease in neurological function (e.g., a 30-degree narrowing of the visual field). Such a specification would provide for both scientific judgment and consistency across tests of different agents.

In some areas of neurotoxicity testing, either form of sensitivity specification appears to be workable. This is the case for tests of basic sensory functions, because there is wide agreement among scientists on functional definitions, and probably also for various tests of motor function. It may also be possible to achieve consensus on the sensitivity of various approaches to neuropathological examinations. Tests of more complex neural function, such as learning, while amenable to specification in terms of positive control studies, provide much greater challenges to other forms of validation. There is still considerable debate concerning the validity of various measures of complex neural function (see ch. 5), and debates over the relative merits of test strategies are likely to persist for some time.

SOURCE: J.S. Young and W.R. Muir, ''Survey of Major Toxicology Testing Laboratories on the Use of Organ Function Tests in Toxicology,' prepared for the U.S. Environmental Protection Agency, EPA contract No. 68-024228, work assignment No. 121415, Washington, DC, September 1986.

September 1985, it sponsored a conference on ''Predicting Neurotoxicity and Behavioral Dysfunction from Preclinical Toxicologic Data, " administered by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology. At this conference, a panel of scientists from academia, industry, and government recommended a two-tiered approach to neurotoxicological evaluations: the first was a screening test, which included either a functional observational battery or a motor activity test, or both, with the use of structure-activity information as appropriate; the second contained more detailed tests, to be conducted on substances that produced neurotoxic effects during any of the fret-tier tests. (These tests are described in more detail inch. 5.) This approach is comparable to the screening required by EPA's OTS guidelines, although the FDA panel did not request direct neuropathological examination.

Since the 1985 meeting, CFSAN has continued to consider revision of the Red Book guidelines for testing of food and color additives. CFSAN scientists considered including some neurotoxicity tests but perhaps not the full range of tests specified in the OTS guidelines. FDA believes that, in order to impose additional testing requirements on industry, it must demonstrate that the tests would increase the

ability to detect neurotoxicants. CFSAN is seeking to demonstrate the utility of proposed neurotoxicity tests by supporting extramural research efforts that focus on neurochemical measures, animal behavior, and measurements of human performance.

The proposed CFSAN guidelines differ from the OTS guidelines in several respects. For example, FDA is reluctant to recommend screening tests that require specific instrumentation, because agency officials believe that requiring industry to procure potentially expensive new instruments would be difficult to justify if less expensive methods would produce adequate data. FDA is also reluctant to require specific neuropathological examinations as screening tests, instead reserving such studies, and behavioral studies requiring instrumentation, as second-tier tests for compounds that give indications of being neurotoxic. Finally, CFSAN is unlikely to include any structure-activity considerations in its proposed neurotoxicity guidelines. CFSAN has yet to develop a specific proposal for a set of neurotoxicity tests or for indicators requiring the performance of such tests.

Suggested Revisions of OECD Toxicity Testing Guidelines

In 1986, EPA, as the designated U.S. representative to the OECD committee for updating toxicity testing guidelines, suggested adding a mammalian neurotoxicity screening battery, which includes elements of the OTS functional observational battery, motor activity test, and neuropathology evaluation (see ch. 5). The new battery would be more generally used, while the OECD's current neurotoxicity guidelines, which specify hen tests, would be used for delayed organophosphate toxicity. In accordance with OECD updating procedures, the proposal was circulated to member countries for review. EPA subsequently revised the guidelines, and the complex OECD procedure for convening expert panels was begun.

CONSISTENCY OF FEDERAL REGULATION OF NEUROTOXIC SUBSTANCES

General Toxicological Considerations

There are numerous differences in regulatory practice under different laws, even within the group of licensing laws (FFDCA, FIFRA, and TSCA). For the most part, these differences do not apply specifically to the regulation of neurotoxic effects, but rather to regulation of all toxic effects. Thus, consistency of regulation for specific neurotoxic effects hinges on consistency of regulation in general (14).

Consistency of Regulatory Requirements

Statutory requirements for chemical regulatory programs differ in several important respects, among them the number of chemicals evaluated, the time available for review, the amount and type of data available at the beginning of the review process, the ability of the reviewer to acquire additional data after review has begun, and the burden of proof regarding safety. For example, the premanufacture notice process under TSCA necessitates review of hundreds of chemicals every year; each review is allotted only 90 days (although an extension is possible), and substantive toxicity data are rarely submitted. EPA can obtain additional data or impose controls on chemicals only if it finds that there may be an unreasonable risk associated with use of the chemical. Indeed, critics charge that the procedural complexities of TSCA incorporated in the statute impose a considerable administrative burden on EPA and render any action under the law difficult. In contrast, under FIFRA, applicants for registration of a pesticide must submit extensive toxicological data and follow specified test protocols, the review process extends over a period of years, the applicant is required to submit additional data if the basic data set raises concerns, and the applicant must establish that the pesticide will be both safe and effective under the proposed conditions of use. Thus, legislation is the root of some regulatory inconsistency, although there is little in legislative language that would preclude a significant increase in intra- and interagency cooperation and coordination.

Consistency of Protection

That there are differences in the degree of scrutiny under different regulatory programs is widely acknowledged. What is less certain is that these differences correspond to differences in the degree of protection offered by the laws and regulations. Often, these disparate requirements reflect real differences in the potential risks posed by the chemicals each program regulates. It maybe that the more intense scrutiny reserved for some types of chemicals is an appropriate reflection of the likeli-

Photo credit: U.S. Environmental Protection Agency

hood that they will harm human health or the environment.

Current laws are generally based on the premise that chemicals for which there is a greater probability of exposure should meet a higher standard of safety. This is most clearly illustrated by explicit prohibition of carcinogenic substances as direct food additives and of pesticides that become concentrated in foods [FFDCA Delaney clause, sec. 409(c)(3), 706(b)(5)(B)]. No such blanket prohibition applies to general industrial or commercial chemicals (regulated under the OSH Act and TSCA), in part because there is less certainty concerning the likelihood of human exposure to many of these chemicals. Some critics of the mechanisms by which industrial and commercial chemicals are regulated argue that these laws do not adequately protect the public's health.

The case is similar for chemicals causing noncarcinogenic toxic effects, which can be divided into chemical classes on the basis of both inherent hazard and expected level of exposure. Chemicals in commerce make up a vast universe—more than 60,000 identifiable chemicals are in EPA's inventory. Many of these chemicals may be present in industrial settings, and a large subset of them is present in consumer products. Pesticides, broadly defined, form a slightly smaller universe, but the number of active ingredients used on foods is much smaller (approximately 600). These differences in the size of chemical classes are reflected in the number of new members of each class introduced each year.

The stringency of the evaluation process for new chemicals under the various laws generally matches the presumption of risk-the combination of hazard and exposure potential-posed by each class and the number of new class members introduced each year. Thus, drugs are not to be permitted to enter the market until proven safe and effective in clinical trials. New pesticides and food additives are evaluated nearly as stringently; however, human trials are not performed. Commercial chemicals, whether intended for industrial or consumer use, receive the least scrutiny.

There are two exceptions to these trends, one minor and one significant. Consumer chemicals

have not received any procedurally different scrutiny than those intended for industrial use, despite the fact that larger numbers of persons may be exposed as consumers than as industrial workers. (EPA does take exposure patterns into account in evaluating chemicals in commerce.) Of much greater potential importance is the fact that cosmetics are not required to undergo premarket toxicity testing. Industry voluntarily tests cosmetics and cosmetic ingredients for acute toxic effects, but few are examined for chronic toxicity. Some have been found to have acute and chronic neurotoxic effects on laboratory animals.

While many scientists find some comfort in the observation that the stringency of review of a chemical matches its presumptive risk (except for cosmetics), public interest groups and others have voiced concerns over such odds playing. The transition of chemical regulation in general from "assurance of safety" to "acceptable risk" remains a source of contention (16). A less comforting observation, even to scientists, is that the stringency of review of a chemical is often inversely proportional to the size of the class of chemicals to be reviewed. For example, chemicals under TSCA make up the largest chemical class, yet they receive relatively little scrutiny under the normal premanufacture notice process. Critics of EPA argue that regulatory resource considerations and a desire not to burden industry, rather than presumptive risk, are in fact driving chemical review criteria. (Economic considerations in regulating toxic substances are discussed in ch. 8.) They raise the question of whether the minimal screening given the majority of chemicals is adequate to deal with high-risk chemicals that are not members of known risk categories (see box 7-H).

Regulation of New v. Existing Chemicals

Existing chemicals in each of the classes considered above are subject to varying degrees of review and reevaluation. In contrast to procedures for reviewing new chemicals, however, procedures for reexamining existing chemicals do not reflect the inherent risks of the chemical classes involved.

Photo credit: U.S. Environmental Protection Agency

EPA attempts to ensure the adequacy of data supporting continued pesticide registration through a regular review process. The registration standards program, which examines 25 chemicals per year, has thus far addressed only a small portion of the active ingredients of registered pesticides. At the present rate, active pesticide ingredients would be reviewed on an average of only once every 12 years. The 1988 FIFRA amendments mandated that the review schedule be accelerated so that *all* active ingredients are reviewed by 1997. To meet this goal, EPA will need to streamline its existing review process. Pesticides suspected of being associated with unusually high risks are examined through a separate special review program. EPA conducts special reviews of 12 to 15 chemicals per year, reaching final decisions on a third of them. Thus, it addresses only a small fraction of the (presumably) high-risk pesticides.

Under section 4 of TSCA, existing chemicals are ranked for probable risk or high exposures before they enter the test rule or consent decree process. In the period from 1977 to 1988, final rules were issued on only 25 chemicals or related sets of chemicals, and consent decrees were reached on three, with nine proposed rules pending. Clearly, these rules address only a very small fraction of the 60,000 chemicals in the TSCA inventory. Evidence that a chemical poses a significant risk must be reported to EPA under section 8(e), but no data need be developed to evaluate the risks of most chemicals. Further evidence comes from sections 8(c) and 8(d) provisions, which require that manufacturers maintain and make available to EPA records of adverse reactions and the results of unpublished toxicological investigations.

Box 7-H—TSCA's Premanufacture Notice Program: Is More Toxicity Testing Feasible?

The thousands of new industrial and consumer chemicals manufactured each year are typically subjected to far less toxicity testing and evaluation under the Toxic Substances Control Act (TSCA) than the smaller number of new pesticide, food additive, and pharmaceutical chemicals registered under other Federal laws. Although TSCA does require a premanufacture notice (PMN) process—all manufactures must notify the Environmental Protection Agency (EPA) before they can begin the commercial manufacture or importation of a new chemical-the statute does not demand that toxicity tests be conducted prior to notification. Consequently, few PMNs include any toxicity information, much less data from specific tests for neurotoxicity. EPA must review PMNs for nearly 2,000 new chemicals each year, and notwithstanding a paucity of data, EPA has only 90 or 180 days (depending on the type of chemical) to examine each PMN and determine whether the new chemical presents a significant risk.

TSCA does grant EPA the authority to require additional testing or to impose restrictions on the use of a new chemical if the Agency determines that the chemical will present an unreasonable risk. EPA has intervened in 10 to 20 percent of the PMNs reviewed annually to restrict the use of the chemicals; most of these actions have been aimed at lowering potential human exposure. In some cases, chemicals were withdrawn from consideration. In other cases, EPA has been successful in requiring manufacturers to conduct significant additional testing.

Critics have decried the lack of more comprehensive testing for this large set of chemicals. They argue that the public health cannot be adequately protected by the minimal testing conducted under TSCA. Why, they ask, doesn't EPA require more testing for toxic effects? It is not because the statute has proven defective: whenever EPA has intervened during PMN review, the Agency has prevailed. Nor is it because scientists in the Office of Toxic Substances (OTS)—the scientists responsible for reviewing PMNs—have substantially different views than their counterparts in other regulatory programs of what constitutes adequate testing.

Testing policies under TSCA are defended on the basis of practical reality: TSCA program officials rebut the charge of insufficient toxicity testing by arguing that the amount of testing being pursued under TSCA is all that can reasonably be required under the circumstances. They note that most new industrial and consumer chemicals have small, uncertain markets and that significant additional testing would cost more than the market for the chemical could cover—in effect banning the chemical based solely on a lack of information about it rather than on any concern or even suspicion about it. Furthermore, OTS scientists point out that EPA does take action against chemicals with high anticipated production volumes (and thus with substantial potential for human exposure) and chemicals suspected of causing adverse effects. Thus, they view the amount of testing of new chemicals being sought under TSCA to be the only feasible amount unless (or until) less expensive, reliable testing methods are developed that could reasonably be sought for a wider number of chemicals.

SOURCE: Office of Technology Assessment, 1990.

FDA's procedures for reviewing existing drugs and food and color additives are less formal than those for pesticides or toxic substances. The Center for Drug Evaluation and Research tracks physicians' reports of adverse drug reactions and relays them to the original evaluators of the drugs. Food and color additives have been notable exceptions to the review of existing chemicals. Until recently, there was no formal monitoring of adverse reactions after an additive was registered. For aspartame, CFSAN established voluntary reporting programs and subsequently requested that physicians and other health professionals inform it of any severe, well-documented reactions associated with foods, food additives, or dietary practices.

Although CFSAN does not require reporting on the use of approved food and color additives, it could track such information and use it to assess the risks associated with approved uses. Under the Priority-Based Assessment of Food Additives Program, a database on uses, levels in food, toxic effects, and chemical structure was created. This system should enable CFSAN personnel to compare new toxicity data to current use patterns or proposed changes in use and to search for predictive trends (e.g., correlations of particular functional groups with toxic effects). Without the ability to actively update information, however, this system may be of limited use for regulatory purposes.

Redundancy of Effort Among Agencies

The definitions of the classes of chemicals addressed in the various statutes have minimized redundancy of regulatory effort. While some chemicals have multiple uses and may be regulated under two or more different laws-e. g., pesticide compounds that also have industrial applications—the different uses dictate different risk evaluations. Under standard-setting and control-oriented laws, toxicity and risk evaluation are usually driven by considerations of probability of exposure; and differences in exposure potential probably preclude redundancy in the evaluation process. Although greater coordination among the standard-setting and control-oriented programs might be worthwhile, available evidence suggests that these programs devote relatively little effort to evaluating toxic hazards and much more to evaluating the risks posed by particular patterns of exposure.

Integration of Effort

EPA is the only regulatory agency discussed in this chapter responsible for implementing a number of very different laws. Other agencies considered in this chapter address only one law or a few closely related laws. The division of labor among regulatory agencies raises the question of how well regulatory efforts are being integrated within and between agencies.

EPA, which is charged with implementing seven regulatory programs under eight of the laws reviewed, does appear to be actively engaged in integrating regulation. Although some integration efforts have been initiated by legislation, the Agency has undertaken a number of initiatives on its own in the recent past. For example, OTS issued a section 4 test rule on chemicals referred by the Office of Solid Waste Management under CERCLA; MCLGs and MCLs have been issued for hazardous waste chemicals that might affect drinking water, even if they have rarely been detected in drinking water; and the drinking water priority list for regulation explicitly includes both pesticides and chemicals listed for priority review under SARA, Another example of recent efforts in regulatory integration is the attempt to produce consistent neurotoxicity test guidelines for both pesticides and toxic substances. Also, EPA is working to consolidate all its risk assessment information into the Integrated Risk Information System (IRIS). Finally, the creation of a discrete Regulatory Integration Division in EPA's Office of Program Planning and Evaluation suggests a commitment to consistent regulation. The creation of a formal neurotoxicity working group, which would indicate an EPA commitment to regulatory integration for the specific concern of neurotoxicity, has been proposed.

There is less evidence of attempts at regulatory integration across Federal agencies than within EPA. There is some collaboration on research but little coordination of regulatory efforts (see app. B). This may be due, in part, to the different-and sometimes conflicting-statutes. Legal requirements for dealing with confidential business information pose barriers to sharing data in some cases; more important is the focus of agency personnel on internal priorities, which does not foster interagency cooperation. The apparent lack of coordination is sometimes quite striking. For example, NIOSH is required by Congress to recommend exposure limits

for OSHA, but OSHA has rarely acted on those recommendations. In its recent rule, OSHA showed a decided preference for values recommended by the ACGIH, despite the fact that NIOSH had established recommended exposure levels (RELs) for 5 of the 20 compounds listed as neuropathic and that four of the five were lower than ACGIH's TLVs. OSHA would be expected, in some cases, to set PELs that were higher than NIOSH's RELs, based on technological and economic feasibility. ACGIH TLVs, however, are derived by a completely different process. OSHA appears to be giving equal or greater weight to the views of a private organization than to those of the agency created to supply it with health assessments.

Specific Neurotoxicological Considerations

Regulatory differences in general strategies for evaluating toxicity entail corresponding differences in the evaluation of neurotoxic effects. Thus for human therapeutic drugs, preclinical toxicity tests are used only to guide observations on clinical trials and to elucidate possible mechanisms of toxicity rather than to assess toxic potential directly. For pesticides and food and color additives, in contrast, animal toxicity data are used directly in predicting human risk. However, even within programs that have essentially similar approaches to assessing toxic risks, there are differences with respect to consideration of neurotoxic risks.

Consistency of Protection

Regulatory programs have adopted one of three basic approaches to toxicity evaluation, depending on which of three underlying assumptions they hold. One approach is based on the assumption that general toxicity tests using high doses are adequate to detect neurotoxic potential and that specific neurotoxicological evaluations are needed only if general tests, data on structural analogs, or other specific knowledge about a chemical indicates a potential for neurotoxicity. Among these are FDA's preclinical testing program for drugs and its current program for approving food additives. The second approach, represented by the pesticide registration program under FIFRA, accepts more general structural information in guiding neurotoxicity testing. All organophosphorous compounds are evaluated for their potential to induce delayed neuropathy, but nonorganophosphorous compounds are not specifically evaluated for neurotoxic potential. All pesticides undergo a general toxicity screen; however, specific neurotoxicity tests are not conducted. Finally, under section 4 of TSCA, specific neurotoxicity testing is required for any chemical with high exposure potential, as well as for chemicals specifically suspected of being neurotoxic. Such testing presumes that standard toxicity tests are not adequate to evaluate neurotoxic effects.

OTA found that Federal efforts to control neurotoxic substances vary considerably between agencies and between programs within agencies. Improving the Federal response will require increased neurotoxicity testing, improved monitoring programs, and more aggressive regulatory efforts.

Whether these different testing procedures correspond to different levels of protection depends entirely on which assumption regarding the sensitivity of standard toxicological tests is correct. Scientists inside and outside of Federal regulatory agencies have expressed a range of opinions regarding the desirability of singling out neurotoxicity as an effect of concern. Many argue that neurotoxic effects cannot be identified without undertaking specific tests. Others argue that there is no more justification for including neurotoxicity tests than for including immunotoxicity (immune system), cardiotoxicity (heart), hepatotoxicity (liver), nephrotoxicity (kidney), or other organ system tests as part of a standard test battery. These scientists believe that general test protocols in which high doses are used will be sensitive *detectors,* if not elucidators, of neurotoxicity. Other scientists argue that potential noncancer health effects in general receive too little scientific and regulatory attention and believe that greater emphasis should be placed on all noncancer health risks.

There is a correlation between the opinions expressed and the actual testing approach of the program in which a particular scientist works. The wide diversity of opinions expressed by knowledgeable scientists reflects individual views on the extent to which existing regulatory programs are protecting public health and the environment from noncancer health risks.

In principle, a study to evaluate whether neurotoxicity testing detects effects that would be missed by conventional toxicity tests is easy to design. However, to be truly predictive for regulatory purposes, such a study would have to address a large number of toxicologically dissimilar compounds. No such study has yet been designed. FDA did sponsor a

review of whether conventional toxicity testing was adequate for the prediction of neurotoxic potential (18). This review consisted of the deliberations of an ad hoc expert panel and a symposium. The panel concluded that explicit neurotoxicological evaluations should be incorporated into toxicity testing, using a tiered-testing scheme. However, its report did not present objective evidence of improvements in test sensitivity as a result of neurotoxicological testing.

As part of its effort to develop neurotoxicity test guidelines, OTS sponsored a retrospective comparison of neurotoxicity tests with standard toxicity tests for chemicals inducing narcosis, as well as a comparison of acute and chronic neurotoxicity tests that addressed a somewhat broader range of chemicals (7,8). The choice of chemicals that induce narcosis tends to bias the comparison in favor of conventional tests, because this effect is relatively easy to detect.

The OTS-sponsored studies found greater sensitivity in acute tests when specific neurotoxicological evaluations were performed-i. e., the lowest observed effect levels were lower for a majority of the 25 compounds evaluated (effects in humans were reported at even lower levels). Considerably greater sensitivity was shown by repeated-dose studies. Some compounds produced qualitatively different neurotoxic effects after repeated dosing, and others showed irreversible effects after repeated, but not acute, tests. Quantitative extrapolation from acute tests was found to underpredict toxicity from repeated exposures. The OTS studies suggest that conventional toxicity tests, especially acute high-dose tests, are not an adequate substitute for neurotoxicological evaluations. The validity of this conclusion for a broader range of compounds has not yet been established.

Coordination Among Agencies

Interviews with toxicologists and neurotoxicologists in various Federal agencies indicated that there has been, until recently, little formal coordination among agencies (see app. B). Regulatory scientists are generally aware of the views of their colleagues in other agencies. There are also several coordinated research efforts mediated by interagency agreements and by personal contact.

Contact among neurotoxicologists at different Federal agencies has not, however, fostered any unanimity of opinion on the best approach to regulating neurotoxic hazards. Real differences of scientific opinion remain, and data that would resolve these differences have not been developed by the agencies involved. Moreover, even within agencies, neurotoxicologists and other toxicologists sometimes disagree on the proper role of neurotoxicity in safety evaluations.

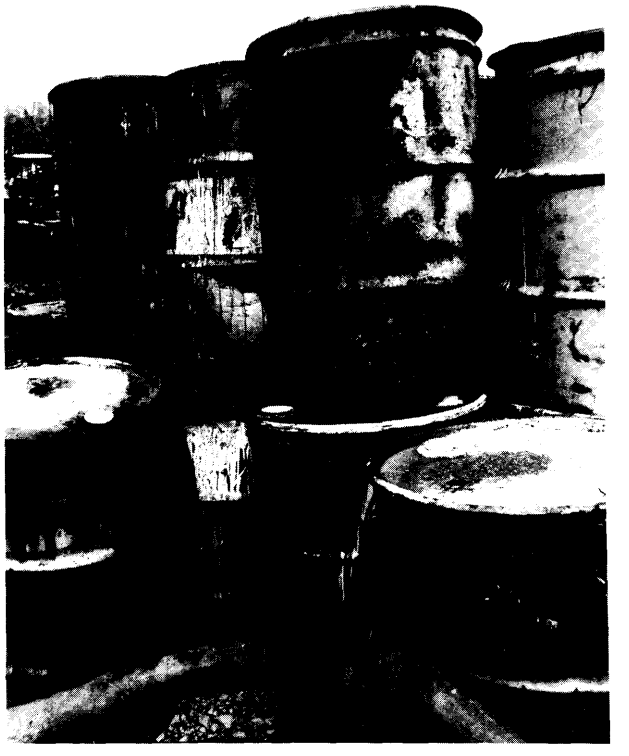

Photo credit: U.S. Environmental Protection ***Agency***

An agency's approach to evaluating neurotoxicity often corresponds to the presence or absence of neurotoxicologists on its staff. Although this presumably reflects personnel considerations-if an agency is not evaluating neurotoxicological data, it does not require people trained to do so-it does raise the question of whether persons who evaluate general toxicological data understand the contributions of directed testing to the prediction of neurotoxic effects. General toxicologists are essential to the review process, but individuals with specialized expertise are often necessary to ensure a comprehensive evaluation. Variations in the perceived need for staff neurotoxicologists reflect a more general problem of toxicological assessment, that of determining the appropriate degree of specialization required to

evaluate the many organ systems potentially affected by a toxic substance.

The Federal regulatory response to neurotoxicity is fragmented not only by differences in scientific judgment, but also by differences in regulatory responsibility. The decision to evaluate drugs, pesticides, and food additives by stricter standards than are applied to commercial chemicals is not based on the views of scientists in regulatory agencies, but on national consensus, as expressed through Congress.

The Value of Establishing a Minimal Data Set

The most striking difference in regulatory programs is between those that require routine testing of all chemicals submitted for review and those that must establish some probability of unacceptable risk in order to require the manufacturer to submit data. These differences tend to reflect both a legislative consensus regarding the hazards posed by different classes of chemicals and the sheer number of chemicals in each class that require review. If neurotoxic effects of chemicals are difficult to predict, it might follow that any regulatory scheme that does not routinely test for neurotoxicity offers diminished or insufficient protection.

If no changes are made in the laws with respect to which kinds of chemicals do and do not require premarket testing, the issue becomes one of whether there is a sound reason to require comparable tests in the several programs that already require premarket testing. Scientists charged with reviewing toxic hazard data in the various programs disagree over the desirability of standardized test guidelines in general, and standardized neurotoxicity evaluations in particular. EPA scientists have argued that standardization provides a distinct advantage for comparing the hazards posed by disparate chemicals, while FDA scientists counter that it is more appropriate to design specific tests to assess expected toxic effects.

These arguments reflect real differences between programs and the power to compel extensive testing. FDA's Center for Drug Evaluation and Research has perhaps the broadest power to compel testing, both preclinical and clinical, and is one of the strongest advocates for flexibility in testing. On the other hand, OTS must undertake arduous rule-making procedures to issue test rules and must carry out protracted negotiations to obtain consent decrees; it is, perhaps, not surprising that OTS was the first regulatory program to issue extensive neurotoxicity testing guidelines. The presence of established guidelines diminishes the number of testing issues that have to be argued in each rule-making or negotiation. The legal constraints on OTS—companies need not conduct any testing beyond what OTS explicitly rules-have favored a more rigid and explicit approach to testing requirements.

There seems to be general, if not complete, agreement among regulatory toxicologists that specific neurotoxicological evaluation is valuable, once evidence of neurotoxicity has been detected. There is also general agreement that such detailed evaluation should not be specified too rigidly but should allow for flexibility in designing tests to fit particular chemicals and to address particular questions.

ADEQUACY OF THE FEDERAL REGULATORY FRAMEWORK

It is important to bear in mind that regulations have implications reaching far beyond the letter of the law. Thus, measuring regulatory effectiveness is only one aspect of gauging the broader set of regulatory *impacts.* For example, regulations impose direct or indirect costs on industry that affect how industry conducts its business. These considerations are addressed in more detail in chapter 8.

Measurements of Effectiveness

Any attempt to measure the success of Federal regulatory agencies in evaluating and controlling the neurotoxic risks posed by chemicals depends on having an independent measure of neurotoxic risks. Finding such a measure is difficult. Two alternatives are considered here. The frost is to compare the proportion of chemicals detected and controlled as neurotoxic substances by Federal regulatory programs to estimates of the proportion of chemicals likely to have neurotoxic effects. The second is to examine evidence of regulatory failures-i. e., misses and false positives.

Expected and Detected Neurotoxicity

It is possible, for at least some regulatory programs, to estimate how many of the chemicals evaluated were reviewed for neurotoxic potential or identified as posing neurotoxic risks. Thus, in the premanufacture notice program under TSCA, approximately 220 chemicals (4 percent of the approximately 5,500 chemicals reviewed during the life-

time of the law) have raised sufficient concern regarding neurotoxicity to merit standard review. Of the 220 chemicals receiving this detailed evaluation, 180 were judged to pose neurotoxic hazards, although in many cases other hazards were judged to be more significant. Due to exposure limitations, only 120 were judged to pose neurotoxic risks. Of these, neurotoxicity was the driving concern in approximately 12 cases.

It is difficult to establish whether the PMN process is truly effective in assessing neurotoxic risk. Generally, toxicity data to confirm the PMN predictions are not available. Reports of significant risk submitted under section 8(e) could be used to identify regulatory failures resulting from inadequate review, but because chemical identities are often claimed to be confidential business information, they are open only to internal scrutiny (see box 7-D).

Of the high-hazard or high-exposure chemicals reviewed under section 4 of TSCA, 19 have been considered for neurotoxicity evaluation since the neurotoxicity test guidelines were issued; three of these were judged not to require neurotoxicity testing during the rule-making or consent decree process. Three additional chemicals were proposed for neurotoxicity testing prior to publication of the test guidelines; one was the subject of negotiated testing, a second was the subject of testing by another program office, and a proposed test rule is under development for the third. Of the chemicals for which the Interagency Testing Committee recommended neurotoxicological evaluation, EPA disagreed on the need for such testing in only two cases; in eight other cases, either testing was in progress or potential exposures were determined to be minimal.

The chemicals evaluated for neurotoxic effects represent a substantial fraction of the total number of chemicals tested under section 4 of TSCA. There are 25 final test rules, seven of which include neurotoxicity testing; nine pending proposed rules, five of

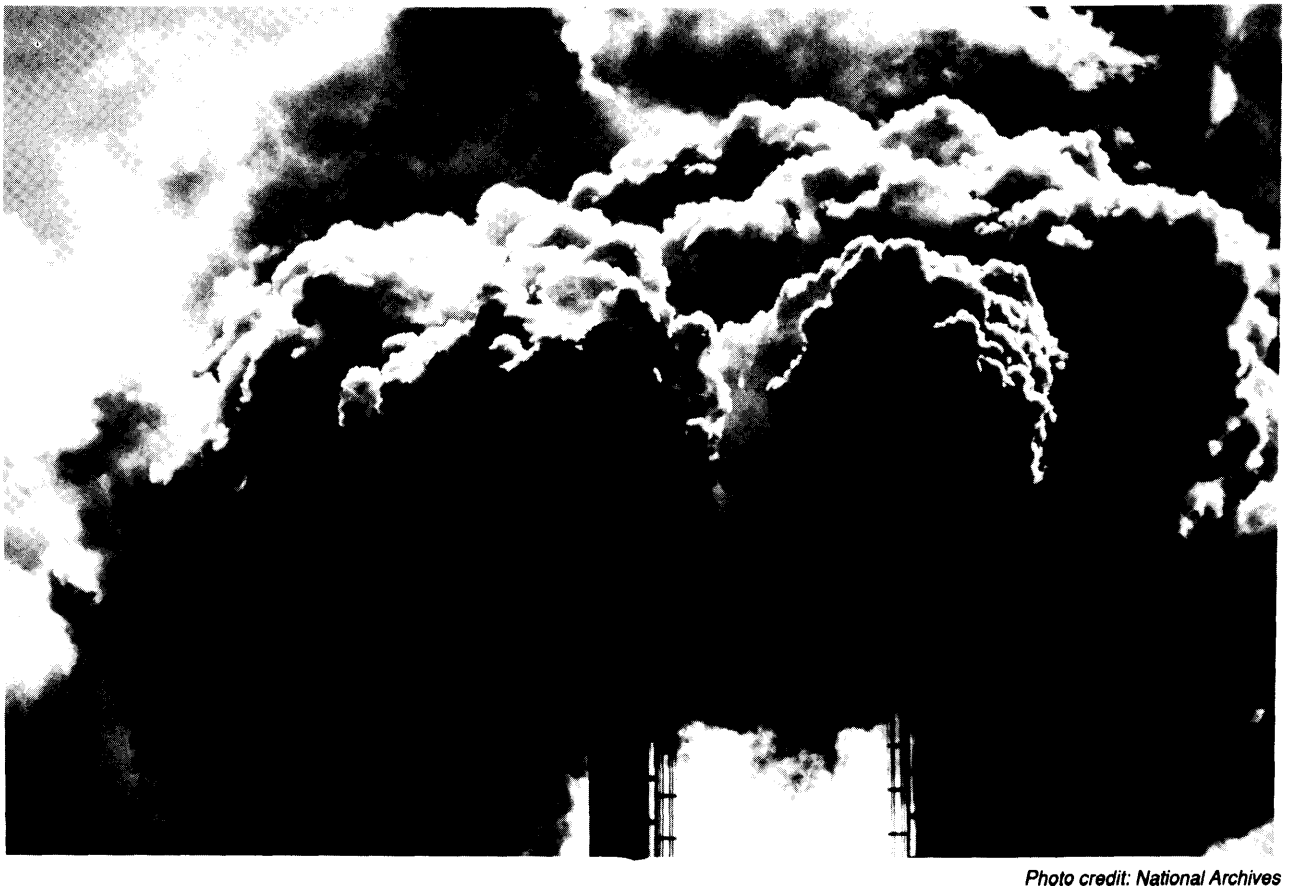

Photo credit: National Archives

which include neurotoxicity; and three consent decrees, two of which include neurotoxicity.

It is more difficult to gauge the extent of neurotoxicity testing conducted under FIFRA.While annual registration totals are available, OPP tracking systems are not yet able to determine the number of chemicals evaluated for adequacy of neurotoxicological data. Only EPN and acrylonitrile could be identified as chemicals for which regulatory action was taken on the basis of neurotoxicity. Other pesticides are being evaluated for neurotoxicity, and data call-ins have been issued, but EPA does not have any accessible record of such data call-ins.

Applications for approximately 330 commercial investigational new drugs are presented to FDA every year; approximately 20 percent of these are eventually approved. In recent years, perhaps 16 percent of the applications submitted have involved neuropharmacological agents. Of the 54 neuropharmacological agents for which FDA reviewed IND applications in 1988, nine were put on hold, two of these because of concerns regarding their toxicity. Only one of these was judged to be neurotoxic.

The FDA annually reviews approximately 60 indirect food additives, 10 direct food additives, and 10 color additives. Many of these involve potential exposures sufficiently low that only the most basic toxicity studies are performed. In the past 5 years, only three chemicals have raised sufficient concern regarding neurotoxic effects to be reviewed by the neurobehavioral toxicity team; this represents less than 1 percent of all applications received.

Under standard-setting or control-oriented legislation, it is not always possible to estimate accurately the proportion of chemicals regulated for neurotoxic concerns, both because the number of chemicals regulated is small and because these laws address chemicals already determined to pose excessive risks. The latest rule proposed by OSHA on permissible exposure limits clearly considers a large number of chemicals (more than 400). Of the approximately 300 for which a basis for a limit was explicitly stated, 20 were indicated as causing nerve damage and 19 as inducing drowsiness. Some neurotoxic chemicals (e.g., methanol) are included in lists for ocular effects, and the list of chemicals regulated for biochemical or metabolic effects includes eight chemicals (out of 26) that inhibit, either directly or indirectly, the production or activity of cholinesterase.

Interpretation of these percentages depends on the proportion of chemicals that would be expected to have neurotoxic effects. Estimates of this proportion have been made by several authors, and they vary widely. For example, Anger and Johnson estimate that there are more than 850 known neurotoxic chemicals (4). Anger (3) reported that 167 of the 588 TLVs promulgated by the ACGIH in 1982 were based at least in part on neurotoxic effects, while Bass and Muir (9) determined that 202 of the 605 TLVs promulgated in 1984-1985 met a similar criterion. In contrast, O'Donoghue (21), summarizing basic toxicity data obtained from Kodak for 448 high-volume chemicals, found only 12 to have primarily neurotoxic effects. Of the 167 chemicals listed by Anger, O'Donoghue found only 28 to have neurodegenerative effects. Differences such as these are also due in part to differing views regarding the definition of neurotoxicity. The estimates given above are not necessarily incompatible. For one thing, they reflect different starting sets of chemicals. For example, ACGIH lists all chemicals for which *some* toxic effect has been noted at or near potential levels of exposure.

Monitoring Mechanisms

An alternative approach to assessing the effectiveness of regulatory programs in controlling neurotoxic hazards is to evaluate the rate of regulatory failure. Unfortunately, while several of the licensing programs have procedures that enable them to track chemicals after approval, these programs have not generally been used to assess the adequacy of the original decisionmaking process.

The registration standards program under FIFRA is aimed at identifying deficiencies in data that resulted from earlier regulatory practice and assumes that current registration practices are appropriate. Reports of adverse reactions to drugs under FFDCA consider a wide range of adverse effects but are generally used on a chemical-specific basis.

Under TSCA, EPA receives and evaluates reports that may indicate significant risks of chemicals in commerce, some of which have been subject to PMN review. These data have not been regularly used to assess the adequacy of the PMN process. EPA has, however, acknowledged the need to review this process. Because EPA is forced to rely substantially on structure-activity analysis, rather than experimental data, in predicting the risks posed

by new chemicals, it has a particularly active interest in assessing the accuracy of its efforts. In 1984, a study was designed to obtain data on a small sample of PMN chemicals that would be representative of chemicals with the highest expected risk (those with intrinsic hazard and high exposure); of these data would be compared with the results of PMN risk assessments to yield an estimate of the accuracy of the PMN process. Unfortunately, although the study was proposed in five versions spanning a wide range of costs, not even the least expensive variant of the study was funded.

Many other statutes, including FFDCA, FIFRA, OSH Act, and the Consumer Product Safety Act, contain similar provisions for reporting adverse effects of chemicals. Any of these reporting requirements could potentially be used to track regulatory effectiveness.

Because EPA is testing chemicals with high production levels (100,000 kilograms in the third year of production) and expectations of significant human exposure, it will be obtaining some data with which to evaluate the accuracy of PMN assessments. These tests will include a functional observational battery and neuropathological measurements, but they will only be carried out for a long enough period of time to measure subchronic effects. This set of tests, taken together, may indicate how the structure-activity predictions used in PMN assessments compare to assessments that have at least a minimal data set.

SUMMARY AND CONCLUSIONS

It is the task of regulatory agencies to limit public exposure to toxic chemicals through programs mandated by law. Because of the great diversity of toxic substances, many statutes exist to control their use. These laws are administered by various Federal agencies, but primarily by EPA, FDA, and OSHA.

New and existing industrial chemicals are regulated by TSCA. Pesticides are controlled by FIFRA, and toxic substances in the workplace are regulated by the OSH Act. The FFDCA regulates food and food additives, drugs, and cosmetics. These laws address the vast majority of toxic substances, and more than a dozen other acts focus on other substances and sources of exposure. Although neurotoxicity is generally not explicitly mentioned in legislation mandating the regulation of toxic substances, it is implicitly included as a toxicity concern.

Regulatory differences in general strategies for evaluating toxicity entail corresponding differences in the evaluation of neurotoxic effects. Thus for human drugs, preclinical toxicity tests are only used to guide observations on clinical trials and to elucidate possible mechanisms of toxicity, rather than to directly assess toxic potential. For pesticides and food and color additives, in contrast, animal toxicity data are used directly in predicting human risk,

Regulatory programs have adopted one of three basic approaches to neurotoxicity evaluation, depending on which of three underlying assumptions they hold. One approach is based on the assumption that general toxicity tests using high doses are adequate to detect neurotoxic potential and that neurotoxicological evaluations are needed only if general tests, data on structural analogues, or other specific knowledge about a chemical indicate a potential for neurotoxicity. Among these are FDA's preclinical testing program for drugs and its current program for approving food additives. The second approach, represented by the pesticide registration program under FIFRA, accepts more general structural information in guiding neurotoxicity testing. All organophosphorous compounds are evaluated for the potential to induce delayed neuropathy, but nonorganophosphorous compounds are not specifically evaluated for neurotoxic potential. All pesticides undergo a general toxicity screen; however, specific neurotoxicity tests are not conducted. Finally, under section 4 of TSCA, specific neurotoxicity testing is required for any chemical with high exposure potential, as well as for chemicals specifically suspected of being neurotoxic. Such testing presumes that standard toxicity tests are not adequate to evaluate neurotoxic effects.

Critics of the regulatory framework voice concern over the odds playing they see in the current process. For example, the chemicals regulated under TSCA make up the largest classes of chemicals, yet they receive relatively little scrutiny by EPA. TSCA does offer options for selecting high-risk chemicals for further scrutiny, but the vast majority of chemicals receive only a limited review. Without significant toxicity data, predicting risk is difficult and must rely on hypothetical relations between chemical structure and biological activity. However, little is

known about structure-activity relationships with respect to neurotoxicity. Critics of EPA raise the question of whether the minimal screening given to the majority of chemicals is adequate to deal with high-risk chemicals that are not members of well-understood risk categories.

OTA found that Federal efforts to control neurotoxic substances varied considerably between agencies and between programs within agencies. This response is fragmented not only by differences in scientific judgment, but also by differences in regulatory responsibility. Moreover, the decision to evaluate drugs, pesticides, and food additives by stricter standards than are applied to commercial chemicals is based not only on the views of scientists, but also on national consensus. Thus, improving the effectiveness of Federal programs depends on many factors, including more public awareness, greater involvement by neurotoxicologists in regulatory program offices, increased neurotoxicity testing, and improved monitoring programs.

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