

Chapter 8

Economic Considerations in Regulating Neurotoxic Substances

“The higher environmental issues rise on the national agenda the more important it is that we have the best possible knowledge of the economic costs of undertaking particular environmental programs *and the costs* associated with *not* undertaking them.”

Russell E. Train
Remarks at the Library of Congress
October 18, 1989

“Although conventional regulatory policies have often worked well, they have also tended to pit economic and environmental goals against each other. These goals should complement one another in the long run if either of them is to be achieved.”

Robert N. Stavins
Environment, vol. 31, No. 1
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“One of the problems in relating economic health and environmental health is that the nation has not developed a quality of life index that measures both. Environmental health factors such as morbidity and mortality, crop and forest damage, soil erosion, air and water pollution, and aesthetic degradation are given little attention compared to such economic health factors as Gross National Product (GNP) and unemployment. Much work needs to be done to develop and use more comprehensive measurements of quality of life.”

An Environmental Agenda for the Future, Island Press, 1985

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Economic Considerations in Regulating Neurotoxic Substances

The fundamental economic consideration in regulating neurotoxic substances involves balancing the economic benefits of utilizing these substances commercially against their actual or potential risks to human health and the environment. The economic benefits include the reduced cost and increased productivity brought about by drugs, pesticides, and chemicals in health care, agriculture, and industry. The risks are the probabilities of increased morbidity, mortality, and environmental contamination stemming from uncontrolled or excessive uses of these substances (35).

Regulations designed to reduce or prevent neurotoxic risks can benefit society by improving public health and the environment. In most cases, however, government and the private sector incur costs in order to achieve these ends. The costs of regulatory compliance may give rise to a number of additional economic impacts, such as increases in market prices, reductions in industry profits, and declines in new product innovation. The problem of balancing benefits, costs, and risks of regulation is not unique to the control of neurotoxic substances; it arises in all forms of health, safety, and environmental regulation.

Many of the key Federal laws under which neurotoxic substances are regulated require agencies to ascertain the positive and negative economic consequences of regulation (see box 8-A). In implementing these laws, Congress has generally intended that agencies prepare regulatory analyses¹ and document the balancing of benefits, costs, and risks of proposed alternatives. It is important to note, however, that Congress typically has not set priorities for the various economic issues arising from regulation, nor has it specified the analytical criteria or procedures that agencies must follow in evaluating the economic impacts of regulation.

The preparation of regulatory analyses of proposals to control neurotoxic substances is a two-step process. The first step, risk assessment, involves

assessing the health and environmental risks posed by various levels of exposure to these substances. Risk assessment provides a scientific basis for regulatory analyses. The second step, risk management, is the end for which risk assessment is conducted (see ch. 6).

One economic consideration in conducting risk assessments is the costs and benefits of acquiring the reliable scientific and technical data needed to regulate neurotoxic substances. Many of these data must be obtained through animal toxicity tests. Two recent evaluations of Federal efforts to regulate neurotoxic substances concluded that there is a need for more neurotoxicity testing of existing and new chemicals (30,43). To date, the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and other Federal agencies with authority to regulate toxic substances have not widely adopted or applied neurotoxicity test protocols (43). Consequently, available neurotoxicity data are insufficient to determine reasonably or to predict the health or environmental effects of all but a few of the substances in commerce that have neurotoxic potential, whether they be pesticides, industrial chemicals, food additives, or drugs.²

More testing of suspected neurotoxic substances will increase the chances of avoiding adverse health and environmental effects. It will also increase development and regulatory compliance costs. Industry and government incur costs in expanding the knowledge base that is essential in regulating toxic substances, but development of this knowledge theoretically improves the precision with which the benefits of regulation can be ascertained. Therefore, the question arises: What is the appropriate economic balance between the costs of neurotoxicity testing and the benefits of the resulting test data in developing regulations?

As discussed in chapter 7, the Federal Government can regulate neurotoxic substances under at least 16 laws. With the exception of regulations to

¹In this chapter, the term “regulatory analysis” refers to analysis used in judging the desirability of a regulation. The term “regulatory impact analysis” (RIA) refers specifically to analysis performed under Executive Order 12291 (46 FR 13191-13196).

²A National Academy of Sciences (NAS) study examined toxicity testing results for a sample of substances that included chemicals in commerce (manufactured in both small and large volumes), pesticides, cosmetics, drugs, and food additives. From a list of 53,500 chemicals, NAS selected a random sample of 675. A random subsample of 100 chemicals with at least minimal toxicity test information was examined in great detail, and conclusions were extrapolated from the review of test data on these 100 substances (30).

Box 8-A—Economic Balancing Provisions of FFDCA, FIFRA, and TSCA

The Federal Food, Drug, and Cosmetic Act (FFDCA), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and the Toxic Substances Control Act (TSCA) are the primary laws under which neurotoxic substances are regulated. Each contains provisions to encourage increased testing for neurotoxicity and to control the production, distribution, and use of substances that present unreasonable risks of neurotoxicity. The following requirements for economic balancing relate to the control provisions in each of these laws.

Federal Food, Drug, and Cosmetic Act—The economic balancing provisions of FFDCA are less explicit than those of the other two Acts. The various sections of the law reflect Congress' intent both to provide for the safety of food (including substances added to food) and to maintain an economically affordable and abundant food supply. Whether regulatory analyses are undertaken depends on which section of the law is being applied and the type of regulatory action being considered. Because of amendments to FFDCA over the years, the regulation of chemicals in food is quite complex (18). Food-related substances addressed under the Act may fall into one or more categories, namely, food, direct or indirect food additives, color additives, naturally occurring environmental contaminants, inherent constituents of raw agricultural commodities, pesticide residues, and animal drug residues.

Finally, procedural considerations are important. The Bureau of Foods does not consider the process of approving and publishing a regulation that permits the safe use of a new food or color additive as formal rule-making subject to the cost-benefit analysis requirements of Executive Order 12291. Proposals to ban or limit the use of food additives that are already approved, however, are regarded as formal rule-making and are subject to the order's requirements. A proposal to establish a formal tolerance for environmental contaminants, a procedure that is rarely undertaken, is also regarded as formal rule-making and would require a cost-benefit analysis.

Federal Insecticide, Fungicide, and Rodenticide Act—In order to register a new pesticide under FIFRA, EPA must ascertain whether it will "cause unreasonable adverse effects on the environment." FIFRA defines these effects very broadly, to include "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*" (7 U.S.C. 136(bb)).

Under section 6 of FIFRA, EPA may cancel, restrict, or suspend the current registration of a pesticide if the Agency determines that the pesticide causes unreasonable adverse effects on the environment when used according to commonly recognized practice. In proposing such action, EPA must take into account the impact it will have on the prices of agricultural commodities, retail food prices, and the agricultural economy.

Toxic Substances Control Act—Section 6 of TSCA gives EPA broad authority to regulate manufacturing, processing, distribution, use, and disposal of chemical substances that present an unreasonable risk of injury to health or the environment. Section 6 states that in proposing any such regulation, EPA must consider and document: the effects of such substance or mixture on health and the magnitude of the exposure of human beings to such substance or mixture; the effects of such substance or mixture on the environment and the magnitude of the exposure of the environment to such substance or mixture; the benefits of such substance or mixture for various uses and the availability of substitutes for such uses; and the reasonably ascertainable economic consequences of the rule, after consideration of the effect on the national economy, small business, technological innovation, the environment and public health.

Congress (42) intentionally did not define "unreasonable risk," but indicated that determining whether a chemical posed such a risk should involve:

... balancing of the probability that harm will occur and the magnitude and severity of that harm against the effect of proposed regulatory action on the availability to society of the benefits of the substance or mixture, taking into account the availability of substitutes for the substance or mixture which do not require regulation, and other adverse effects which such proposed action may have on society.

Congress further elaborated on the extent to which economic analysis was needed in the balancing process:

The balancing process described above does not require a formal benefit-cost analysis under which a monetary value is assigned to the risks associated with a substance and to the cost to society of proposed regulatory action on the availability of such benefits. Because a monetary value often cannot be assigned to benefit or cost, such an analysis would not be very useful.

Congress cited the National Academy of Sciences (27) as support for the last statement.

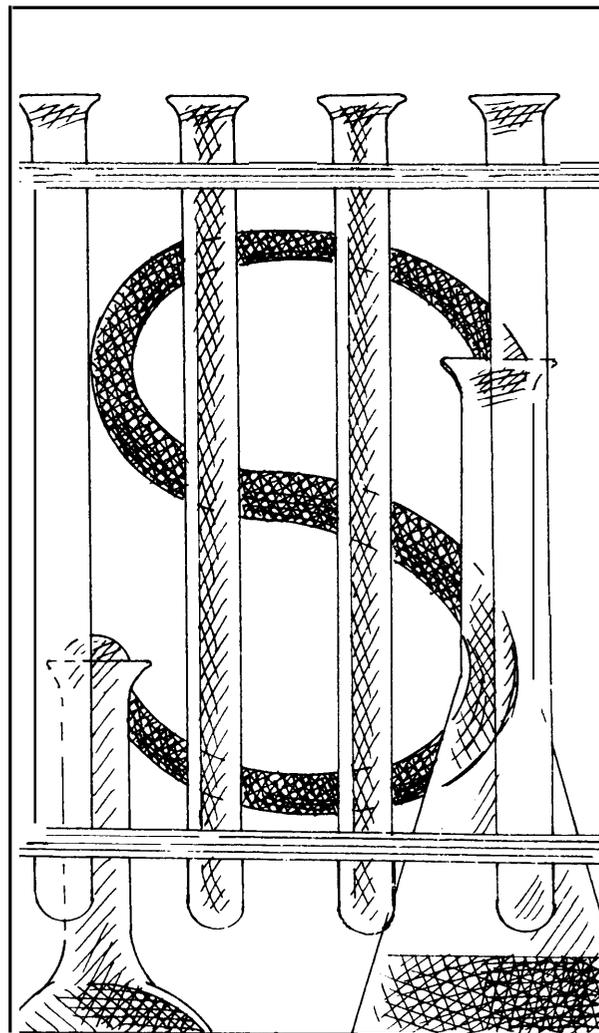
SOURCES: Office of Technology Assessment, 1990; U.S. Congress, 1976; Hattan, 1983; National Academy of Sciences, 1975.

reduce human exposures to lead,³ the greatest amount of regulatory activity specifically directed toward neurotoxic concerns has occurred under three laws: the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended by the Federal Environmental Pesticide Control Act (FEPCA) (7 U.S.C. 135-136y); the Toxic Substances Control Act (TSCA) (15 U.S.C. 2601-2629), as amended; and the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 301-392). Each of these laws provides authority to obtain scientific and other data on which to assess risks and to control the use of toxic substances.

As with their assessments of health risks, agencies differ greatly in their approaches to evaluating and balancing the economic impacts of regulation. EPA, for example, has developed rigorous guidelines for evaluating the costs, benefits, and alternatives of regulations having major economic consequences (19). At the other end of the spectrum, FDA, in regulating food additives, carries out balancing in a less formal, more qualitative manner (22,25).⁴ These differences reflect differences in legislative requirements for balancing benefits, costs, and risks (see box 8-A), as well as differences in agency views on the applicability of Executive Order 12291 (46 FR 13191), which defines current policies and requirements for the executive branch in evaluating regulatory proposals (see box 8-B).

The purpose of this chapter is to examine and evaluate several salient economic issues involved in regulating neurotoxic substances. Economic issues that arise from requirements to test for neurotoxicity as well as from restrictions on production and use of neurotoxic substances are discussed. Also discussed are the different forms of regulatory analysis that agencies have applied in addressing these issues.

Economic issues are common in the regulation of all toxic substances, regardless of the health endpoints of concern. However, since (with the exception of lead) the regulatory record for neurotoxic substances is limited, the present discussion is general in scope. No attempt has been made to present a comprehensive economic evaluation of the costs and benefits of a test rule or use regulation for a specific neurotoxic substance. Nor has an attempt



Illustrated by: Ray Driver

been made to conduct a technology assessment of the impacts of regulating a class of neurotoxic chemicals.

ECONOMIC ANALYSIS OF REGULATIONS AFFECTING TOXIC SUBSTANCES, PESTICIDES, AND DRUGS

As noted above, current laws for controlling neurotoxic substances do not specify which analytical procedures Federal agencies must use in evalu-

³Regulations to reduce occupational and environmental exposures to lead have been promulgated under at least 10 different Federal statutes (28).

⁴An exception occurs in the regulation of food additives that are known or suspected carcinogens. Under the 1962 Delaney amendment to FFDCA (21 U.S.C. 348(c)(3)(A)), the use of these substances in any quantity is prohibited, regardless of the impact on food costs or supply or any offsetting benefits of use (25).

Box 8-B—Requirements of Executive Order 12291

President Ronald Reagan signed Executive Order 12291 in 1981 (46 FR 13191) to increase agency accountability for regulatory actions. To achieve this goal, the order specifies that, in promulgating, reviewing, or developing regulations, all agencies, to the extent permitted by law, adhere to the following requirements:

- Administrative decisions shall be based on adequate information concerning the need for and consequences of proposed government action.
- Regulatory action shall not be undertaken unless the regulation's potential benefits to society outweigh its potential costs to society.
- Regulatory objectives shall be chosen to maximize the net benefits to society.
- Among alternative approaches to any given regulatory objectives, the alternative involving the least net cost to society shall be chosen.
- Agencies shall set regulatory priorities with the aim of maximizing the aggregate net benefits to society, taking into account the condition of the particular industries affected by the regulations, the condition of the national economy, and other regulatory actions contemplated for the future.

The regulatory impact analysis (RIA) is the means for ensuring that agencies meet these requirements. The Order requires that agencies submit RIAs to the director of the Office of Management and Budget at least 10 days before publication in the Federal Register of a notice of proposed rule-making or final rule. For major rules, a preliminary RIA must be prepared and submitted at least 60 days before publication of a notice of proposed rule-making, and a final RIA must be submitted at least 30 days prior to publication of a final rule. A major rule is any regulation that is likely to have an annual effect on the economy of \$100 million or more, to result in a major increase in costs or prices, or to have significant adverse effects on competition, employment investment, productivity, innovation, or the competitiveness of domestic firms relative to foreign counterparts.

SOURCE: Office of Technology Assessment, 1990.

ating the economic impacts of regulatory decisions. Regulatory agencies have not interpreted statutory requirements to evaluate proposed regulatory alternatives as imposing certain limits on the scope or approach of analyses that are undertaken. Instead, agencies like EPA have adapted various evaluative approaches, depending on the regulatory and economic issues involved.

The executive branch, through the Office of Management and Budget (OMB), has independently developed and implemented a requirement that agencies produce specific kinds of economic evaluations for regulatory actions that have major economic impacts. The current OMB requirement for regulatory impact analysis of such actions has evolved through a series of executive orders, and the OMB has incorporated the Regulatory Impact Analysis (RIA) requirement into its executive oversight function (see table 8-1).

This section examines four economic issues and the analytical approaches agencies have applied in addressing these issues as they have emerged in decisions to regulate toxic substances.

Costs, Benefits, and Economic Efficiency

Thus far, the terms “costs” and “benefits” have been used in a generic sense to indicate negative and positive economic impacts of regulation. Although this usage is correct, it is important to recognize that, for the purposes of analysis, these terms are narrowly defined to have specialized meanings. The precise operational definitions depend on the type and scope of analysis and the economic issue being assessed.

Accordingly, cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) have come to refer to analytical techniques in which macroeconomic analysis serves as the basis for evaluating the positive and negative economic consequences of a program or decision. For both techniques, costs refer to the resource inputs required to implement a program. Benefits and effectiveness refer to program outputs. Costs are computed in dollars, using values that the resource inputs would have had in alternative uses—their opportunity cost. In cost-benefit analysis, program consequences are also evaluated in dollar terms. In cost-effectiveness analysis, program consequences are measured in natural or physical units.

Table 8-I—The Institutionalization of Regulatory Analysis, 1971-81

Act. Executive Order	Year	Title	Type of analysis
OMB memo 10/5/71	1971	Quality of Life Review	Costs, benefits
Executive Order 11821	1974	Inflation Impacts Statement	Costs, benefits, inflationary impacts
Executive Order 11949	1976	Economic Impact Statement	Costs, benefits, economic impacts
Executive Order 12044	1978	Regulatory Analysis	Costs, economic consequences
Regulatory Flexibility Act	1980	Regulatory Flexibility Analysis	Impacts on small businesses
Executive Order 12291	1981	Regulatory Impact Analysis	Costs, benefits, net benefits

SOURCE: Office of Technology Assessment, 1990.

In the application of cost-benefit and cost-effectiveness techniques to evaluate health and safety regulations, costs and benefits are generally defined and measured from the perspective of achieving intended regulatory objectives of risk reduction. Cost-benefit or cost-effectiveness analysis is employed to evaluate whether the benefits of a regulation exceed its costs, or whether a regulation is cost-effective. That is, are the resources required to implement regulations being utilized in an efficient manner? The concept of economic efficiency refers to gains derived from resources allocated to achieve stated objectives.

In cost-benefit and cost-effectiveness analyses of toxic substances regulations (e.g., premanufacturing approvals, test rules, and use restrictions), the costs consist of those resources expended for the purposes of regulatory development, implementation, and compliance. They include expenditures by both government and the private sector. Government incurs expenses in: 1) developing regulatory procedures, including toxicity test methods, test rules, and chemical production, distribution, and use restrictions; 2) reviewing premanufacture notices (PMN), registration, and other requests by industry to produce and sell new chemical substances; and 3) carrying out necessary monitoring, inspection, and enforcement responsibilities.⁵ The private sector usually bears compliance costs, which consist of labor, materials, equipment, and other expenses for: 1) obtaining premanufacturing approvals; 2) conducting animal toxicity tests,⁶ keeping records, and submitting reports on chemicals of concern; and 3) altering production processes and products to conform with production, distribution, and use restrictions.

Evaluation of the benefits of controlling toxic substances involves first assessing the effectiveness of regulation in achieving risk reductions. Risk reduction is measured as reductions in mortality, morbidity, and ecological dysfunction that would occur as a consequence of changes in exposure to toxic chemicals. In cost-effectiveness analysis, benefits are measured in natural units, such as years of life saved, incidence of disease averted, and days of work loss avoided. In cost-benefit analysis, risk reductions are evaluated in monetary units.

Net efficiency refers to the difference between benefits and direct costs, or the difference between the value of reductions in health, safety, and environmental risks achieved through regulation and the value of the resources employed to achieve those reductions. It is important to note that the efficiency criterion of cost-benefit and cost-effectiveness analyses does not encompass any positive or negative impacts that regulation may have on industry employment, profits, or new product innovation. Other forms of economic analysis, some of which are discussed below, are utilized in assessing these so-called secondary economic impacts of regulation.

Under sections 4 and 5 of TSCA (15 U.S.C. 2604 and 2605), EPA typically has not conducted cost-benefit or cost-effectiveness analyses in implementing test rules or reviewing PMNs. The economic costs of complying with individual test rules for existing chemicals or production prohibitions for new chemicals are generally relatively small;⁷ they are not likely to reach the \$100 million per year specified by Executive Order 12291 for a major rule. Furthermore, analysis of the health and environmental benefits achieved by these actions can be

⁵In practice, it is difficult to apportion the government's program costs to individual proposals. Consequently they are often omitted from analysis.

⁶Estimates of the costs of conducting animal toxicity tests that include certain neurological evaluations are presented later in this Chapter.

⁷Even when the total costs of complying with test rules are small, they may represent a significant portion of the sales revenues for low-volume, specialty chemicals. As discussed below, EPA recognizes the distributive effects of test rule costs in an analysis of impacts on market prices and profits.

speculative. To quantify these benefits, many assumptions must be made about a chemical's rate of market penetration, projected sales volume, types of uses, and likely disposal practices.

Under section 6 of TSCA (15 U.S.C. 2605), EPA considers all aspects of formal cost-benefit analysis in evaluating the impacts of a proposed regulation (48). The balancing language of section 6 (box 8-A) encourages cost-benefit analysis whether or not a regulation is likely to have major economic impacts. Since the enactment of TSCA, however, EPA has promulgated only a handful of regulations under section 6 (41).⁸

EPA's Office of Toxic Substances recently completed a preliminary risk assessment for environmental and occupational exposures to acrylamide, in which risks for carcinogenic reproductive effects and neurotoxic effects were evaluated (49). Although this assessment may lead to use restrictions that are based on neurotoxicity, further action by EPA under section 6 is contingent on reviews of the acrylamide risk assessment by the Occupational Safety and Health Administration and other agencies having potentially applicable regulatory authorities.

Under FIFRA, EPA's decisions to approve new pesticide registrations or to cancel, suspend, or alter existing registrations are not regarded as rule-making that is subject to the cost-benefit requirements of Executive Order 12291 (48). However, because of the specific balancing language of sections 3(c) and 6(b) of FIFRA (box 8-A), EPA has developed a methodology for evaluating the economic impacts of registration decisions. This procedure is discussed in the next section.

For pesticides that are applied in the production, storage, or distribution of raw agricultural commodities, part of the registration process may include an EPA review to establish a tolerance under FFDCA [21 U.S.C. 346a(b)]. EPA's granting of such a tolerance is considered rule-making, but cost-benefit analyses of these decisions are not developed, because all of the economic consequences of a tolerance are regarded as positive. Finally, the revocation of a pesticide tolerance by EPA is also considered rule-making. Although cost-benefit eval-

uations are developed for these decisions, they have been of limited utility in the regulatory development process.

Although few WA'S to control neurotoxic substances have been conducted, EPA has conducted cost-benefit studies of regulatory proposals to reduce human exposures to lead under other environmental statutes. Under the provisions of the Clean Air Act for regulating fuel additives [42 U.S.C. 7545(c)], EPA developed a cost-benefit analysis of several options for phasing out the use of lead additives in gasoline (39). In addition, EPA has evaluated the economic benefits of options for reducing lead in community water supplies under the Safe Drinking Water Act (42 U.S.C. 300f-j) (23). Both studies estimated the health benefits of reducing lead's neurotoxic effects in children.

Risks and Benefits

A second economic issue that arises in regulating chemicals, pesticides, and drugs concerns balancing the economic benefits of a substance that are lost through a restriction or ban on its use against the risks of continued use at unregulated levels (27,29). Risk-benefit analysis is used to address this issue.

As noted above, in a cost-benefit analysis of chemical regulation, the benefits consist of improvements in public health and environmental quality that would result from restricting the use of toxic substances. However, in risk-benefit analysis of licensing and approval regulations, in particular under FIFRA and FFDCA, the term "benefit" has acquired a different meaning. In this instance, benefits are defined in terms of the opportunity cost of switching to substitutes for the chemical in question. In registration decisions for agricultural pesticides, for example, EPA's Office of Pesticide Programs assesses benefits in terms of changes in the value of crop yields and pest control costs (29). Similarly, in approving new drugs, FDA assesses benefits in terms of therapeutic efficacy.

Risk-benefit analysis recognizes that, on the one hand, chemicals, pesticides, and drugs generate economic benefits that manifest themselves in the form of increased output and lower product prices. On the other hand, the increased use of toxic

⁸One reason for limited regulatory activity under sec. 6 is that EPA regards TSCA as the regulatory authority of last resort. Under TSCA sec. 9 (15 U.S.C. 2608(b)), for example, EPA must provide other appropriate Federal agencies with the first opportunity to regulate substances that present unreasonable risks.

chemicals may introduce more of these substances into the environment, at the time of initial use or subsequently in waste disposal. The risks to health and the environment from increased exposures to toxic chemicals, therefore, may also increase.

Risk-benefit analysis can also be used to compare the change in environmental and health risks to the change in economic benefits resulting from regulation. If the use of an existing chemical is increased, the analysis compares the potential increase in risks with the anticipated increase in benefits. If the use of a chemical is reduced, the analysis compares the expected reduction in risks with reduction in benefits.

EPA initiates risk-benefit analysis for proposed restrictions on pesticide use when it receives toxicity data that trigger questions about potential risks to human health. Although these analyses may be done when new compounds are preregistered, they are typically undertaken in response to toxicity data generated through the special review process for existing pesticides (see ch. 7). When special review leads to proposed use restrictions or suspension or cancellation of a registration for an agricultural pesticide, for example, analysts estimate the health risks and net values of crop production for projected uncontrolled and the proposed controlled applications of the pesticide. The risk-benefit ratios for these scenarios are then compared in assessing the economic impact of the proposed regulation.

The 1988 amendments to FIFRA call for an accelerated review of pesticides that were first registered under the pre-1972 FIFRA guidelines (1). Because this group includes a number of widely used agricultural insecticides that function by attacking the nervous systems of target organisms, it is likely that special reviews will trigger some risk-benefit evaluations for neurotoxicity.

In conducting risk-benefit analysis of new drugs, FDA is more qualitative in its approach. In ascertaining the benefits, FDA distinguishes between the efficacy and the effectiveness of the candidate chemical. Efficacy refers to the ability of the substance to alter the symptoms or pathological

condition for which it was developed. Effectiveness refers to the degree of reduction in disease or death, and hence in health-care expenditures, a drug might achieve when optimally prescribed and taken. FDA weighs test evidence of adverse reactions to the drug (risks) against its demonstrated therapeutic properties (benefits). The 1962 amendments to FFDCA (Public Law 87-781) require that manufacturers submit sufficient data to demonstrate a new drug's efficacy but not its effectiveness.

Impacts on Market Prices and Industry Profits

A third issue of economic importance that arises in the regulation of toxic substances concerns the impact of the direct costs of regulation on market prices and industry profits. Although industry initially pays the compliance costs of regulation, it attempts to pass these increases on to customers in the form of higher product prices. Higher prices may, in turn, discourage sales and reduce industry profits. If there is a major expansion of regulations covering a broad range of industrial and commercial activities, as there was in the 1970s, the costs of regulation may contribute to the Nation's rate of inflation.⁹

TSCA stipulates that EPA consider "the relative costs of the various test protocols and methodologies" when implementing chemical test rules [section 4(b)(1); 15 U.S.C. 2603(b)(1)]. In 1980, with the first test rule issued under section 4 (45 FR 48524-48566), EPA outlined procedures for estimating the relative costs of test protocols and the projected impact of these costs on the marketability of the chemicals to be tested. These procedures remain in use today (24,40). EPA evaluates the impact of anticipated testing costs for each manufacturer or processor by estimating unit¹⁰ test costs and then comparing these unit values to the market price of the chemical. A market analysis may be conducted to assess four key features of the market for the chemical being tested: 1) responsiveness of demand to changes in price; 2) expectations for market expansion or decline; 3) industry cost characteristics; and 4) industry structure (40).

⁹OMB and the Reagan Administration emphasized the cumulative inflationary effects of regulation in implementing Executive Order 2291.

¹⁰Unit test costs are estimated by first computing the annualized value of total direct test costs and then dividing by the annual supply (i.e., production and imports) of the chemical. In annualizing test costs, EPA uses the expected product lifetime for the annualization period and the estimated cost of capital in the chemical industry for the annualization rate. If available, sales volume information is used in estimating expected product lifetimes. Product lifetimes are longer for commodity chemicals (i.e., chemicals with multiple uses and large-volume sales) than for specialty chemicals. If sales volume data are unavailable, EPA uses a 15-year annualization period. The Agency currently uses 7 percent as the annualization rate (1 1).

Table 8-2-Comparison of Licensing and Notification Mechanisms

Factor affecting incentives to innovate	Licensing (FIFRA or FDCA)	Notification (TSCA)
Burden of proof	Fails on innovating firm	Initial burden falls on regulatory agency
Agency's authority to compel testing of new products	Withhold approval until desired information is submitted	Requires agency finding that a product may pose an unreasonable risk
Burden of delay	Fails on innovating firm	Falls on public

SOURCE: Office of Technology Assessment, 1990.

EPA uses an informal rule of thumb to determine adverse economic impacts of testing. If the unit costs of testing a chemical are less than 1 percent of the price of the chemical, then the potential for adverse economic impact due to the test rule may be low. Conversely, if the unit test costs exceed 1 percent of price, then the potential for adverse economic impact may be high (24).

Regulation and Incentives for Innovation

An issue that is related to the impact of compliance costs on profitability is the effect of regulation on incentives for innovation. The development and introduction of new chemicals, pesticides, and drugs have produced benefits in virtually every area of human need: food, health, shelter, clothing, transportation, communication, and energy. On the other hand, extensive use or misuse of these substances has increased risks to public health and the environment. Hence the question, "Does regulation to protect health and the environment alter industry's incentives to develop new drugs and chemicals?"¹¹

Companies develop and introduce new products as a means of competing in a given market and making a profit. Profitability depends on sales volumes and the cost and time required to develop, produce, and market new products. It also depends on the availability of competing products and patents and other factors that protect the market position of the innovating company. Finally, because there is uncertainty surrounding each facet of the development and commercialization of new products, innovation in the private sector will take place only if the prospective reward-risk ratio is considered favorable.

Regulation can affect each of these factors. First, the compliance costs of regulation increase the costs of developing new products. Second, the regulatory process adds to the time required to develop and introduce new products. Third, use restrictions can limit the market for a product, or in the extreme case of a ban, eliminate the market altogether. Fourth, reporting requirements may lead to the disclosure of proprietary information that may compromise the competitive position of the innovating company. Finally, because regulation can add uncertainties regarding costs, delays, protection of proprietary data, and so on, it adds to the financial risk of developing new products.

An important aspect of how a regulation affects incentives for innovation concerns the manner in which the regulatory process acts as a barrier to the commercialization of new products. In this regard there are important differences between the pre-market screening requirements of TSCA versus those of FIFRA and FDCA. The key difference is in the way the prescreening process assigns the burden of proof to demonstrate that a new product does or does not pose unreasonable risks (see table 8-2). Under the notification requirement of TSCA, the burden falls on the regulatory agency to make a finding that a product may pose an unreasonable risk. Under the licensing mechanisms of FIFRA and FDCA, the burden falls on the innovating company. The regulatory agency can withhold approval for marketing of a new product until it is satisfied that the firm has conducted sufficient testing to establish that the product poses no unreasonable risks.

Numerous studies have sought to assess the aggregate effects of Federal regulatory changes on

¹¹A related but analytically more complicated issue concerns whether the impact of health and safety regulations on incentives to innovate produce a net gain or loss to society. The temporal framework for analysis must be long enough to consider the positive and negative impacts of emerging chemical and drug technologies under various levels of regulatory control. Regulatory analyses usually lack this perspective. Risk-benefit analysis of proposed pesticide controls, for example, usually focuses on short-term economic impacts (3 to 5 years) and considers only currently registered chemical and nonchemical controls as alternatives (31).

innovation in the drug, pesticide, and chemical industries.¹² These studies have measured changes in an industry's innovative efforts in terms of the resource inputs and outputs of the innovative process. Measures of inputs into innovation have included: total research and development (R&D) expenditures per year; R&D expenditures as a percentage of annual sales or profits; time from initial discovery to commercialization; and development cost per new chemical entity. Typical output measures have included the number of new products registered or licensed per year and effective patent lifetimes. These measures have been examined before and after implementation of a change in a regulatory program or a change to ascertain whether there are significant quantitative differences. Although it is beyond the scope of this chapter to evaluate these studies critically, it is useful to summarize their findings and discuss some of the difficulties encountered in measuring the impact of regulation on innovation in the chemical, pesticide, and drug industries.

One difficulty in using total R&D expenditure measures has been the difficulty of distinguishing between R&D costs of truly new compounds (i.e., new chemical entities or new active ingredients for pesticides) and costs of new applications and combinations of previously discovered compounds. A second difficulty is that a substantial amount of the R&D expenditures for testing new chemicals is integral to their development. For pesticides, for example, toxicity testing and metabolism and residue studies are essential in understanding the properties and mechanisms of action on target organisms. Similar test information is needed in drug development. In other words, there is considerable overlap in the generation of test data needed to develop an application for a new substance and data needed to ensure its safety.

Drug R&D Studies

The most studied area of regulatory impact on innovation to date has been the effects of the 1962 amendments to FFDCA on R&D in the pharmaceutical industry. For the most part, studies agree that the overall rate of new drug introductions declined substantially from the 1950s to the 1960s and even more into the 1970s (see, e.g., 15,17,32,51). Studies

have shown that development time and cost to manufacturers increased significantly after enactment of the 1962 amendments (see, e.g., 7,20,26,38).

Although these studies demonstrate consistent, adverse effects on drug innovation after a change to a more stringent regulatory regime, they do not agree on the relative importance of regulation as a factor in these impacts. Other influences not related to regulation, for example, declining drug research opportunities and exogenous increases in R&D costs, have been hypothesized as being partially responsible for the observed declines in drug innovation during this period. U.S. data showing that the decline in new approvals was already under way before 1962 and international data demonstrating comparable trends in other countries tend to support the conclusion that regulation has been only partially responsible for these declines (15).

Pesticide R&D Studies

Although there have been no studies of how regulatory efforts directed specifically toward neurotoxicity have affected pesticide innovation, there have been studies of the aggregate effects of pesticide regulation on R&D. A study by the Council on Agricultural Science and Technology (8) found that from 1968 to 1978—before and after enactment of the 1972 amendments to FIFRA—direct costs of bringing anew pesticide to market increased, delays from discovery to registration grew, and the composition of R&D expenditures shifted from synthesis, screening, and field testing to registration, environmental testing, and residue analysis.

Studies conducted by EPA (5) found little evidence of a reduction in pesticide innovation that could be attributed to EPA regulatory requirements. This conclusion was corroborated in an unpublished OTA study (45). OTA reported that after 1972, total pesticide industry R&D expenditures continued to grow at the same rate as pesticide sales. In addition, there was no apparent trend in pesticide registrations over the period 1966 to 1980 that could be attributed to regulation.

Chemical R&D Studies

In the late 1970s and early 1980s, prior to EPA's issuance of a final rule for premanufacturing notices

¹²For recent reviews of studies of the impact of Federal regulations on innovation in the drug, pesticide, and chemical industries, see refs. 16,19,31.

(PMNs),¹³ many parties expressed concern that the major economic effect of section 5 of TSCA would be to reduce innovation by chemical companies (46,37,36). Several studies were conducted to estimate the impacts of the PMN process on the introduction of new chemicals (see, e.g., 3,37). Impacts were assessed for several alternative PMN filing formats proposed by EPA and were dependent on the direct costs of preparing and submitting the PMN as well as the indirect costs of delays and uncertainty associated with the ultimate disposition of the PMN.

One of the difficulties in assessing the impacts of the PMN rule on innovation in the chemical industry is that data on the number of new chemicals introduced annually, prior to the implementation of the PMN rule, are quite limited. It has not been possible, therefore, to establish a good baseline against which to measure the rate of chemical innovation since implementation of the rule.

EPA's estimates of direct filing costs for the final PMN rule were rather nominal (\$3,000 to \$18,000 in 1983 dollars per new chemical introduction) (19). However, some parties, notably the Chemical Specialties Manufacturing Association, argued that even costs in this range would have a disproportionate distributional impact on introductions of small-volume chemicals (19). Some of the smaller-volume, lower-value chemicals are not able to absorb even the relatively low compliance cost burdens represented by these estimates.

Utility of Regulatory Analyses in Devising Environmental Regulatory Policy

It is the need to document the economic impacts and potentially high costs of Federal regulatory decisions that continually motivates agencies to evaluate the effectiveness of these decisions. The goal in conducting these evaluations has been to improve regulatory decisionmaking through systematic development of information, preferably quantitative information, about the positive and negative economic impacts of proposed regulations.

From an analytical point of view, the ability of any evaluative technique to influence the selection of a particular regulatory alternative depends on the degree to which that technique can provide clear-cut distinctions among alternatives. Because of large gaps in underlying scientific information, estimates of costs, risks, and benefits are more often than not quite crude and highly uncertain. Consequently, cost-benefit and other regulatory analysis techniques are approximate and capable usually of distinguishing only between clearly superior and clearly inferior alternatives.

Improving Regulations

Despite their limitations, cost-benefit and cost-effectiveness analyses have influenced the development of regulations. In a recent assessment of impact analyses for 15 major regulations, EPA concluded that cost-benefit analysis had improved individual environmental regulations by:

- guiding the development of the regulation (i.e., showing that net benefits increase or decrease if the proposed regulation is made more or less stringent);
- leading to the specification of additional alternatives for analysis and consideration;
- eliminating alternatives that are clearly not cost-effective;
- adjusting alternatives to account for differences between industries or segments of industry; and
- supporting decisions (i.e., showing that there are net benefits for a regulatory decision that have been formulated under a different decision framework).

EPA noted that in some cases it is precluded by law from allowing the results of a cost-benefit analysis to influence rule-making.¹⁴ In some of these instances, the Agency has prepared cost-benefit analyses anyway, to conform with the requirements of Executive Order 12291.

The General Accounting Office, in reviewing the utility of cost-benefit analysis at EPA, noted this difficulty and recommended that the Agency forward its analyses to Congress, since they could still

¹³Although the statutory requirements for premanufacture notification and review (15 U.S.C. 2604(a)(1)(A)) do not stipulate that these processes must be stated in a rule or that the information be provided in a particular form, EPA (19) determined that the issuance of a PMN rule was in the best interest of all concerned parties. Toward this end, the Agency began operating the PMN program on an interim basis in July 1979. The final rule establishing PMN requirements and review procedures was not issued until 1983 (48 FR 21742).

¹⁴Under the Clean Air Act, for example, primary national ambient air quality standards must be based solely on health effects, without consideration of benefits, costs, or economic impacts (42 U.S.C. 7409(b)(1)).

provide useful information for congressional oversight (41). EPA supported this recommendation but noted that care should be taken in interpreting the findings because of the uncertainties and gaps in data that are likely to exist (48).

Additional Contributions

EPA noted several other contributions that cost-benefit analysis has made. As the Agency has gained experience in quantifying benefits, it has been able to transfer analytical expertise from one regulatory area to another. For example, part of what EPA learned from evaluating the health benefits of removing lead from gasoline has been applicable in estimating the benefits of reducing lead in drinking water.

Application of the cost-benefit approach has improved the consistency and comprehensiveness of regulatory analyses of proposed rules. Evaluation of regulations to control pollutants that have the same health outcome (e.g., cancer) has encouraged more uniformity in analyzing data on health effects. For multimedia pollutants, the application of cost-benefit analysis has increased awareness that regulatory action against pollution of one medium has ramifications for human exposures to pollutants in other media.

Economic Principles of Cost-Benefit and Cost-Effectiveness Analyses

As indicated above, cost-benefit and cost-effectiveness analyses seek to quantify and compare the economic inputs and outputs of a regulatory decision. If cost-benefit analysis confirms that the net benefits (i.e., the benefits minus the costs) of a regulatory proposal are positive, the regulation is said to produce an economically efficient allocation of resources. Thus, implementation of that regulation will result in a net economic gain to society.

Concepts and Definitions

In general, the concepts of cost-benefit and cost-effectiveness rest on the basic economic concept of opportunity cost: that is, the true cost of any activity consists of the value of alternative endeavors that might have been undertaken with the same resources. For example, the opportunity cost of premarket testing of a chemical is the value that resources used for toxicity testing would have had if used in production, sales, or other research activities.

The principal technical distinction between CBA and CEA, as noted earlier, is that CBA benefits are valued in monetary units, whereas CEA benefits are valued in natural, or nonmonetary, units. Because all costs and benefits are measured in the same units in CBA, this technique can be used to compare similar or widely divergent types of decisions. Thus CBA might be used to compare different regulatory options such as protective labeling, use limitations, or a total product ban. In the health area, analysts frequently prefer CEA to CBA because of the difficulty or undesirability of placing a dollar value on life. When using CEA to evaluate health programs that have both mortality- and morbidity-reducing consequences, analysts must often compare noncommensurable outcomes. How are two programs to be compared when one saves several lives but has a limited impact on morbidity, while the other saves a few lives and has a more extensive impact on illness? To address this problem, analysts have developed a measure called quality-of-life-adjusted years.

Cost-effectiveness is useful in making relative comparisons among regulatory options, and it is more meaningful when two or more alternatives are compared. For example, instead of considering the cost-effectiveness of toxicity test A standing alone, analysts examine the cost-effectiveness of test protocol A compared to protocol B or protocol C. Protocol A is cost-effective if it yields the required test data at a lower cost than protocol B or C; or A is cost-effective if it produces more useful data than B or C when the same level of resources is utilized in each test protocol. In both of these comparisons, protocol A would be regarded as the most economically efficient alternative of the three (economic efficiency is also a relative concept and refers to the alternative that provides the greatest return for a given level of resource expenditures).

THE COSTS OF NEUROTOXICITY TESTING

Animal toxicity testing and the resources expended for this purpose are now considered essential features in the development of new chemicals and drugs. FFDCA and FIFRA require demonstration of the ability of drugs and pesticides, that is, of the designed toxic properties, to attack diseases or target organisms. The relative safety of a drug (as measured in terms of unintended toxic effects) or a

pesticide (as measured in terms of morbidity or mortality to nontarget organisms) must also be demonstrated. TSCA emphasizes establishing a minimal set of information about a chemical's toxic properties before it is introduced into commerce. Under TSCA, manufacturers can also be requested to provide additional test data if there is cause to believe that a chemical may present an unreasonable risk to human health or the environment (see ch. 7).

Over the years, Federal authorities responsible for regulating chemicals have paid attention primarily to the potential carcinogenic, mutagenic, and teratogenic effects of pesticides and toxic substances. Although concerns regarding neurotoxic effects were occasionally mentioned, in most cases they were of secondary importance. With steady advances in the field of neurotoxicology and corresponding improvements in the ability to understand and to test for the neurotoxic effects of chemicals, the adverse effects that a substance may have on the nervous system have become of increasing interest and importance in regulatory decisionmaking.

In order to gauge the economic significance of requirements for increased neurotoxicity testing, this section discusses factors in the costs of animal tests for neurotoxicity. Estimates obtained by the Office of Technology Assessment (OTA) of the costs of conducting certain neurotoxicity tests are then presented. Finally, the incremental effects that the costs of neurotoxicity testing will have on total R&D costs for new chemical technologies are discussed.

Determinants of the Costs of Toxicity Tests

The costs of animal toxicity tests vary greatly from laboratory to laboratory. Many factors contribute to these variations, but they can be placed into two categories: *scientific*, or differences in protocol requirements, laboratory personnel, facilities, and so on; and *financial*, or differences in laboratory costs, rates, and fees.

Scientific Determinants

There are five major scientific considerations that determine the costs of any toxicity testing: protocol requirements, quality assurance, personnel, laboratory capabilities, and laboratory automation. Each of these is discussed below.

Protocol Requirements—The requirements of the test protocol are the single most important factor

in determining the costs of toxicity testing. Of these requirements, duration of exposure has the greatest impact on costs. Tests to identify the adverse effects of acute exposures are usually completed within 1 month; tests for chronic exposures may require up to 2 years of animal dosing and observation. Because of the time difference alone, direct labor costs may differ by as much as a factor of 40.

Route of exposure is the next most important cost factor in protocol design. Because of the relative ease of dose administration, oral exposure via gavage (force-feeding) is least costly, followed by oral feeding, dermal exposure, and inhalation exposure. Dermal and inhalation exposures require special preparations and equipment. Inhalation also requires special monitoring equipment to measure the concentration of the test substance in the air breathed by the animals.

Although EPA has promulgated toxicity testing guidelines (50 FR 39397-39470), these protocols are not rigid recipes. Chemical manufacturers may exceed EPA requirements (e.g., an increased number of dosage groups or animals per group) or suggest additional testing based on previous experience and test findings.

Quality Assurance-Quality assurance affects the costs of toxicity testing in proportion to the accuracy and precision of the measurements required by the protocol. To achieve greater accuracy, more effort is needed in controlling contamination or other factors that may bias measurements. To achieve greater precision, more effort is needed in making duplicate measurements and analyses.

Federal good laboratory practice guidelines and regulations have, for the most part, required laboratories to establish in-house quality assurance units. The number of persons in these units varies by laboratory. Some laboratories do not have full-time quality assurance personnel and rely on outside consultants or part-time personnel, whose costs may be lower. Laboratories with large quality assurance units perform functions well beyond the basic test requirements, and their costs usually are much higher.

Quality assurance personnel perform protocol evaluations, general laboratory inspections, evaluation of technical procedures, verification of raw data, interim and final report audits, and verification of the final report. The time required for these procedures

varies with the degree of automation at the laboratory, the degree of report standardization and computerization, the amount of data audited (which may range from 10 to 100 percent), and the experience and efficiency of the personnel.

Personnel—The levels of professional and technical expertise required for a particular toxicity test can significantly influence costs, particularly in acute studies. The education and experience required may be specified by the protocol, Federal regulatory requirements, or general consensus, any of which will result in cost variations. Smaller laboratories may have only limited personnel available for performing the tests (i.e., senior scientists may be performing procedures that would normally be done by technicians).

Laboratory Capabilities-Cost may also vary with mix of capabilities within a laboratory. Many laboratories do not perform the full complement of required test functions (i.e., analytical chemistry or electron microscopy) in house. Laboratories that use consultants or subcontractors to perform these functions increase costs by adding general and administrative fees. Laboratories that have extensive in-house capabilities but do not operate at full capacity incur greater overhead.

Laboratory Automation-There are major cost differences between manual and automated methods of data collection. Highly sophisticated, on-line computer systems can capture data electronically, lowering facility and animal monitoring costs. Examples include automatic control, monitoring, and recording of environmental conditions within the laboratory, as well as computerized data stations for animal body weights, food consumption, and clinical observations.

Financial Determinants

Four financial factors influence laboratory costs: 1) overhead rates, 2) general and administrative rates, 3) fees, and 4) labor rates.

Overhead Rates-Overhead costs are the indirect expenses, such as rent, heating, lighting, equipment, computer services, telephone, insurance, and so on, associated with the operation of a laboratory. Overhead costs are usually computed as a percentage—called the overhead rate—of total direct labor costs.

Overhead rates vary significantly among laboratories, for numerous reasons. Geographical location

can affect overhead rates through variation in utility costs; rent, land, or construction costs; property taxes; State income taxes; and Federal corporate income taxes. The number of years the commercial laboratory has been in business may influence its overhead rate. Newer firms typically have a smaller work force, a large capital investment in new equipment, and sizable expenses in order to generate new business. Older, established firms often support a significant portion of employees on overhead, offer a better benefits package, and buy more up-to-date instrumentation.

The overall capabilities offered by a laboratory also affect the overhead rate. The more varied the capabilities, the more equipment and personnel are required. On the other hand, laboratories with more limited capabilities must hire consultants and subcontractors to perform certain tests, which may be quite expensive.

General and Administrative Rates-General and administrative costs represent the salaries of administrative and support personnel who do not engage in the study, but whose functions are essential to the operation of the laboratory. Examples include management, personnel, accounting, contracts, marketing, and legal employees. Usually, commercial laboratories have general and administrative rates of 5 to 25 percent of total direct labor costs. The more established laboratories tend to have higher general and administrative rates because of higher ratios of support to nonsupport personnel.

Fees—Fees refers to the profit expected from a study. Due to the confidential nature of such information, it is difficult to obtain data on fees received by commercial laboratories, but they range from 5 to 40 percent.

The wide range in profits may reflect marketing strategy and the volume of studies being performed. If volume is low, lower fees may be charged to attract new business. To encourage volume testing, many laboratories will also offer discounted prices for multiple testing packages. These package deals may be significantly lower than the sum of the unit costs for each of the individual tests in the package. Furthermore, acute toxicity protocols are often bid at or below actual cost in order to encourage future business.

Labor Rates-Labor rates vary substantially from one laboratory to another, depending on the mix of

individuals required to conduct a specific test. Salaries for similar types of technical positions also vary with regional economic conditions.

Cost Estimates for Neurotoxicity Testing

Because experience with neurotoxicity testing is still relatively limited, there is considerable uncertainty regarding testing costs. Recently, in support of the TSCA Test Guidelines Program, EPA (50) prepared estimates for several toxicity testing protocols that include neurotoxicity testing. These estimates were constructed by a senior toxicologist who is experienced in managing contract laboratory operations for toxicity testing. Because of the uncertainty regarding the representativeness of test cost estimates that are essentially from one source, it was decided as part of this study to obtain independent estimates of the costs of neurotoxicity testing.

To obtain these estimates, OTA surveyed researchers in several industrial, government, and contract laboratories (35). Researchers were selected on the basis of their experience in neurotoxicity testing, not the type of laboratory in which they work. Because the potential pool was small, it was not possible to obtain enough individuals to represent in a statistically valid way each of the three laboratory settings.

The chief purpose of the survey was to obtain a better understanding of the range of costs for animal tests to characterize the neurotoxicity of a specific chemical. A questionnaire was prepared to obtain cost estimates for acute, subchronic, and chronic toxicity tests of a single chemical that include various neurological evaluations. Cost estimates were requested for acute, subchronic, and chronic toxicity tests augmented with four neurotoxicity tests: functional observational battery, motor activity, neuropathological evaluations, and schedule-controlled operant behavior. (See ch. 5 for a description of these tests.) Duration and route of exposure were specified for each protocol. The protocols for which cost estimates were solicited are indicated in table 8-3.

In addition to total costs for each test protocol, respondents were asked to provide separate estimates of the incremental costs for each of the four neurotoxicity tests. The purpose was to assess how much each type of neurotoxicity test would contrib-

ute to total test costs and whether neurotoxicity test requirements would lead to substantial increases in costs. This information is not available in the EPA estimates (50).

The ranges for the different test cost estimates that were obtained from this survey are presented in table 8-4. These are the highest and lowest cost estimates for the indicated toxicity tests and the highest and lowest incremental cost estimates for each of the added neurotoxicity tests. As expected, estimates of acute toxicity test costs are lower than those for repeated-dose studies, and estimates of costs for tests using the oral route of exposure are lower than those for tests using the inhalation route.

Median cost estimates for each of the base test protocols and each of the added neurotoxicity tests are presented in table 8-5. (Because this kind of survey is likely to yield outliers at both the high and low ends of distribution, the median is the preferable estimate.) The median estimates indicate that a complete set of core neurotoxicity tests, including a functional observational battery, motor activity, and neuropathology, may add from 40 to 240 percent to the cost of conventional toxicity testing of a single chemical. The major portion of the added cost is due to the requirements of the neuropathological examinations. Based on its survey, OTA found that acute neurotoxicity tests (including EPA's functional observational battery, motor activity test, and neuropathology evaluations) are likely to add a total of about \$50,000 to standard toxicity test costs of a single chemical. Subchronic neurotoxicity tests may add up to \$80,000, and chronic tests may add well over \$100,000. The EPA subchronic schedule-controlled operant behavior test (which is only likely to be done after the other neurotoxicity tests) may add about \$64,000. However, the functional observational battery alone would add only \$2,500 to the cost of a conventional acute toxicity test. The added cost impact is highest for the acute test protocols. A conventional acute test involving oral exposure costs about \$21,000.

EPA median cost estimates (50) are considerably lower than OTA survey estimates for identical protocols—from one-half to nearly one-fourth. Although the EPA estimates were developed approximately 6 months before the OTA study, the 1988 inflation rate of 4 to 5 percent during this period does not account for differences of this magnitude.

Table 8-3-Protocols for Which Cost Estimates Were Solicited

Protocol	Neurotoxicity Test			
	Functional Observational Battery	Motor Activity	Neuro-pathology	Schedule-Controlled Operant Behavior
Acute inhalation	x	x	x	
Acute oral	x	x	x	
Subchronic inhalation	x	x	x	
Subchronic oral			x	x
Subchronic oral	x	x	x	
Chronic oral	x	x	x	

SOURCE: Office of Technology Assessment, 1990.

Table 8-4-Ranges in Cost Estimates for Animal Toxicity Tests Combined With Neurotoxicity Evaluations for 1988 (thousands of dollars)

Protocol	Toxicity Test Base Cost	Neurotoxicity Test (incremental costs)			
		Functional Observational Battery	Motor Activity	Neuro-pathology	Schedule-Controlled Operant Behavior
Acute inhalation	\$8.8-47.2	\$11-213	\$1.2-12.3	\$4.7-187.6	NA
Acute oral	6.9-39.7	1.1-21.3	1.2-11.3	4.7-179.6	NA
Subchronic inhalation	99.1-391.0	2.9-32.9	2.1-11.8	6.2-362.9	NA
Subchronic oral	69.5-183.0	2.7-32.9	2.1-11.8	6.2-271.5	NA
Subchronic oral (NP & SCOB)*	69.5-183.0	NA	NA	6.2-271.5	11.0-80.3
Chronic oral	234.0-783.9	3.8-85.8	4.8-38.2	11.3-602.0	NA

*Neuropathology (NP); schedule-controlled operant behavior (SCOB)

SOURCE: Office of Technology Assessment 1990.

Table 8-5-Median Cost Estimates for Animal Toxicity Tests Combined With Neurotoxicity Evaluations for 1988 (thousands of dollars)

Protocol	Toxicity Base Cost ^a	Neurotoxicity Test (incremental costs)				Median Total Increment ^a	Increment as a Percent of Base
		Functional Observational Battery	Motor Activity	Neuro-pathology	Schedule-Controlled Operant Behavior		
Acute inhalation	\$ 26.6(7) ^a	\$ 2.5(5)	\$ 4.5(6)	\$42.0(5)	NA	\$ 49.9(5) ^b	188
Acute oral	21.2(7)	2.4(5)	4.4(6)	42.0(5)	NA	49.9(5)	235
Subchronic inhalation	190.6(7)	4.8(5)	4.7(6)	42.0(5)	NA	79.1(5)	42
Subchronic oral	111.0(7)	4.8(5)	4.7(6)	29.7(5)	NA	79.1(5)	42
Subchronic oral (NP & SCOB)*	109.8(5)	NA	NA	41.7(4)	64.1(5)	87.0(4)	79
Chronic oral	308.0(6)	12.5(5)	19.8(6)	59.7(5)	NA	113.2(4)	37

^aNumber of observations shown in parentheses.^bBecause of incomplete responses, columns do not add to total.

*Neuropathology (NP); schedule-controlled operant behavior (SCOB).

SOURCE: Office of Technology Assessment, 1990.

NEUROTOXICITY TEST COSTS AND INNOVATION

In order to assess the impacts of testing for neurotoxicity on innovation in the drug, pesticide, and chemical industries, it is essential to describe the patterns of innovation for drug, pesticide, and chemical products. While there are certain similarities among the three, there are important economic

differences between the development process for new chemicals and that for new drugs or pesticides.

Drug and Pesticide Development

There are many similarities in the process of developing new drugs and pesticides. The key factors governing the pattern of innovation in these industries are the high costs and long development times experienced from discovery of a new compound to commercialization of it. Hundreds of new

compounds may be screened for each new pesticide and drug that is eventually marketed. Approximately 10 years may elapse from discovery to first registration (31,33). The pharmaceutical industry estimates that it currently costs well over \$100 million to develop, test, and bring to market a **new** drug product (52). The pesticide industry estimates development costs for a new pesticide of about \$25 million, with another \$25 to \$50 million required for building and equipping production facilities (4).¹⁵

Agrichemical and pharmaceutical companies spend from 9 to 15 percent of sales revenue on R&D (31,33). Most R&D in pesticide and pharmaceutical companies is internally financed and conducted in order to protect the proprietary status of new innovations. The disadvantage of this practice is that uncertainties imposed by the regulatory process, either as delays in the introduction of new products or as unexpected limitations or bans on the sale of these products, may reduce the return on industry's investments in research.

The high costs and long time from discovery to commercialization force the development process for new pesticides and drugs toward those applications that are likely to have very high returns. Only a relatively small number of markets are large enough to make it economically worthwhile for firms to develop these products. Consequently, pesticides are developed and initially registered for major uses, for example, on crops such as corn or soybeans. Subsequently, they are tested for use on minor crops.

The actual discovery of a new drug entity—a new chemical with therapeutic potential—is just the first step in a lengthy process of R&D. The discovery phase of the process consists of chemical synthesis and animal testing to establish a compound's toxicology and pharmacology. The development phase encompasses clinical testing to assess potential toxic effects in healthy humans and, subsequently, to establish in patients the therapeutic efficacy of a new drug candidate.

The average effective period of patent protection for a new chemical entity declined between 1966 and 1979 (16). The estimate of 9.5 years of protection is about one-half the maximum period of patent protection of 17 years. This decline in patent life,

which has been largely attributed to longer development and regulatory approval times, became a major policy issue in the early 1980s. Congress addressed the problem in 1984 with the Drug Price Competition and Patent Restoration Act (Public Law 98-417). This law allows restoration of part of the patent protection time that elapses during development and FDA approval.

The recent estimate of \$125 million (1986 dollars) as the total research and development cost for an approved new drug is based on new drugs approved between 1970 and 1985 (52). The increasing costs of developing new drugs are due in part to an increasing focus on therapies for chronic conditions. The development of drugs of this kind requires more extensive testing (33).

Neurotoxicity Tests and Innovation in Drugs and Pesticides

The above discussion of the processes for developing drugs, pesticides, and chemicals provides a framework within which the innovation impacts of conducting animal tests for neurotoxicity may be assessed. The impacts of testing on innovation depend on overall test costs, duration of the tests, and the timing (scheduling) of the tests within the innovation period.

One possibility would be for the animal toxicity tests with combined neurological evaluations to take place during the preclinical and pre-field testing phases for drug and pesticide development, respectively. In this scenario, the additional costs of testing for neurotoxicity would occur during the second or third years of a 10-year developmental period.

If neurotoxicity test protocols are totally incompatible with other concurrent animal toxicity testing, then the additional costs of obtaining neurotoxicity data would be the capitalized value of the full test costs at the expected date of marketing approval. The expected date of marketing approval is 7 to 8 years in the future. At the assumed 10 percent rate of interest, the capitalized value of \$190,000—the median cost estimate for subchronic oral toxicity testing with functional observation, motor activity, and neuropathology evaluations—is from \$370,000 to \$430,000. The capitalized value of \$420,000—the median cost estimate for chronic oral toxicity testing with the same neurotoxicity evaluations—is from

¹⁵These amounts appear to be in line with earlier detailed estimates by Goring (14) of the costs of commercializing a new pesticide.

\$820,000 to \$900,000. These amounts are small, compared to current estimates of total capitalized costs of developing a new drug or pesticide.

A second possibility would be for neurotoxicity test data to be requested at the very end of the drug or pesticide development process. In this instance, timing of the tests is of much greater importance than their costs. Testing that, for example, extends the innovation period by 1 year at the end of the development period has an associated opportunity cost equal to the interest on the total cumulative R&D investment. For drugs and pesticides, the costs of delaying marketing approval at this point clearly overshadow any outlays required to conduct the tests.

Neurotoxicity Tests and Innovation in Chemicals

The pattern of new product innovation in chemicals is considerably different from that of drugs or pesticides (45). For one thing, there is greater diversity among chemical products, which include plastics, solvents, fibers, detergents, catalysts, and basic organic and inorganic chemical feedstocks. More important from an economic perspective, however, is the fact that new drugs and pesticides are developed for quick penetration into large markets. In contrast, the initial market for the vast majority of new chemical products is very small, and failure rates are high. Markets for large-volume chemicals develop slowly over a number of years.

Data on the number of new chemicals introduced annually into commerce before TSCA are uncertain. Estimates of the rate of new chemical innovation range from 700 to 1,400 compounds annually (3,12). Of these, as many as 70 percent were estimated to have annual production volumes of less than 1,000 pounds, which is regarded as a threshold level of output for a viable commercial product (3). Furthermore, many low-volume products were, in all likelihood, developed and marketed by very small firms in the business of "custom-manufacturing" chemicals. Since the implementation of the final PMN rule in 1983, the annual receipt of PMNs by



Photo credit: U.S. Environmental Protection Agency

EPA has increased steadily, to nearly 1,700 compounds in 1986 (6).

Under section 5 of TSCA, EPA does not require that chemical manufacturers conduct toxicity testing prior to submission of a PMN; manufacturers are only required to supply any health or environmental test data that are available at the time of submission. Although EPA can request additional toxicity testing of new chemicals, it has used this authority sparingly.¹⁶ In a recent analysis of 8,000 PMNs received by EPA from July 1979 through September 1986, fewer than one-half contained toxicity test data (6).

Although data are not readily available on the average costs of developing and introducing a PMN chemical, as noted above, many of them are produced and marketed as specialty products. Expected profits from the sale of small-volume chemicals

¹⁶If, in reviewing the PMN submission, EPA decides the chemical may present unreasonable risks to health or the environment, the agency can limit production and utilization of the substance while more test data are developed (15 U.S.C. 2604(e)). If EPA decides the chemical will present unreasonable risks, the agency can require the development of additional test data (15 U.S.C. 2604(f)). Auer and Gould reported that EPA had ordered submission of more test data for about 200 PMN chemicals from 1979 to 1986. An additional 150 PMNs had been subject to voluntary actions, some of which involved testing. Finally, 164 chemicals were voluntarily withdrawn by the submitted when presented with the likely prospect of conducting more testing (6).

cannot, in most cases, cover the costs of extensive testing, especially if there are substitute products already on the market. Thus, a request for neurotoxicity testing, which could add substantially to costs of testing currently being done, could lead to a reduction in the rate of innovation in certain classes of low-volume products, particularly those that are vulnerable to even modest regulatory compliance costs.

ECONOMIC BENEFITS OF REGULATING NEUROTOXIC SUBSTANCES

It is important to distinguish between the adverse effects of neurotoxic substances and the benefits of reducing or “preventing these adverse effects. The adverse effects of neurotoxic substances are expressed as impacts on human health and the environment and are measured in terms of mortality, morbidity, disability, and environmental damage. They should include effects on mental status, such as memory loss and cognitive dysfunction, that may be associated with exposures to neurotoxic substances.

Reducing or preventing the risks of exposure to neurotoxic substances means reducing the magnitude of these adverse effects. The human and monetary values placed on risk reductions are a measure of the benefits of regulation. In the economics of health and safety, several approaches have been used to assign monetary values to reduced risk of mortality, morbidity, and disability. These approaches have been broadly categorized as valuation through adjudication (jury awards), political processes, individual preferences, and resource or opportunity costs.¹⁷ Valuation through resource or opportunity costs will be discussed here.

Knowledge Requirements for Estimating Benefits

To estimate the benefits of policies to reduce or prevent neurotoxic risks requires knowledge and quantification of the following:

- . the relationship between economic activities and the rates of use of neurotoxic substances;
- . the relationship between the environmental fate and transport mechanisms that determine ambi-

ent environmental concentrations and, hence, human exposures to these substances;

- the relationship between the activities of individuals (e.g., eating, working, exercise) and the rates of human intake of these substances;
- the biological mechanism by which these substances cause disease in humans; and
- the relationship between changes in health status and the utilization of health care.

Only the first and the last of these relationships are basically—although not exclusively—in the realm of economics. The intervening ones represent the interface of science and economics—in particular, they are the substance of risk assessments of exposures to neurotoxic substances (35).

The fact that exposures to neurotoxic substances result in more effects and more varied effects on health than, say, exposures to carcinogens is an important distinction and one that poses analytical difficulties in risk assessment and benefits analysis. In contrast to carcinogenicity, which can usually be characterized as a single outcome with discrete measures of health status (i.e., the disease is present or it is not), neurotoxicity may be manifested as multiple effects, each of which may produce a continuum of health states ranging from mild to severe.

The Health Costs of Neurotoxicity

As noted above, the opportunity costs of morbidity and mortality that can be attributed to neurotoxicity provide a measure of the potential economic benefits of reducing neurotoxic risks to human health. These opportunity costs, frequently called the social costs of illness, include direct and indirect costs of illness and death. The direct costs of illness consist of the payments for health-care products and services utilized in providing patient care. The indirect costs of illness encompass the expected earnings an individual loses as a result of not working. Medical care costs and foregone earnings are estimated for each year from the onset of illness to expected year of death. This time stream of costs is then discounted to present values.

Estimating benefits in this manner is known as the productivity, or human capital, approach. Most economists regard this approach as providing lower-

¹⁷Valuation according to individual preferences, or willingness to pay, is frequently cited by economists as the most appropriate measure of the value of reducing the risks of adverse health effects (13).

Table 8-6--Personal Health-Care Expenditures for the 10 Most Expensive Medical Conditions in the United States in 1980 (millions of dollars)

Medical condition	All ages	Under 65	65 or over
Diseases of the circulatory system	\$33,184	\$13,078	\$20,015
Diseases of the digestive system	31,755	26,084	
Mental disorders	20,301	14,612	5,689
Injury and poisoning	19,248	15,042	4,206
Diseases of the nervous system and sense organs	17,499	13,028	4,471
Diseases of the respiratory system	17,305	13,164	4,141
Diseases of the musculoskeletal system and connective tissue	13,645	9,821	3,824
Neoplasms	13,623	8,302	6,322
Diseases of the genitourinary system	13,162	10,721	2,441
Endocrine, nutrition metabolic system, and immunity disorders	7,656	4,689	2,968

SOURCE: U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, *Health United States*, 1983, DDHS Pub. No. (PHS)84-1232 (Washington, DC: U.S. Government Printing Office, 1983)

bound estimates of the benefits of improving health because it does not attempt to measure and include the disutility experienced by persons having these diseases or by their families and friends. This kind of disutility is particularly relevant for dementia, retardation, and other mental disorders in which neurotoxicity may be a causative or contributing factor.

The Costs of Mental Disorders and Diseases of the Nervous System

Mental disorders and diseases of the nervous system contribute substantially to health costs in the United States. In 1980 (the most recent year for which costs of illness were estimated for specific disease categories) they ranked as the third and fifth most expensive medical conditions, respectively, in terms of personal health-care expenditures (table 8-6). The estimate of nearly \$40 billion (1980 dollars) for these two categories of morbidity does not include values for lost productivity, restricted activity, and other social costs (e.g., rehabilitation for drug and alcohol abuse) that may accompany mental illness or other forms of cognitive and behavioral impairment.

The Costs of Neurotoxicity As an Element of Dementia

Dementia is defined as the loss of intellectual function. It is manifested as a complex of symptoms that can be caused by as many as 70 underlying conditions. The causes of disorders that produce the vast majority of dementia cases are still not understood (44); however, some dementias may be caused or exacerbated by neurotoxic substances in prescription drugs, metals, solvents, and other chemicals

(21). Other dementia diagnoses include necrosis of brain tissue due to vascular obstruction, various infectious diseases, tumors, and toxicity from alcohol (21).

Although the costs of dementia to the Nation can be only crudely approximated, they are high and are bound to increase as the population ages. Estimates of the costs of dementia are presented here as a basis for estimating the health costs of neurotoxicity. One study has estimated that at least 2 to 3 percent of dementia patients were diagnosed as having disorders involving drug toxicity (21). If this can be regarded as a lower-bound estimate, then from 2 to 3 percent of the costs of dementia may be taken as a lower-bound estimate of the social costs of neurotoxicity. Applying 2 to 3 percent to each of the above estimates for the overall costs of dementia yields estimates of \$0.5 billion to \$1.5 billion annually for neurotoxicity alone.

The Costs of Exposure to Lead

Epidemiologists have demonstrated associations between excessive lead exposure, particularly during childhood, and several kinds of adverse neurological and behavioral effects.¹⁸ In the past, public health agencies focused principally on severe lead exposure and the resultant symptoms of overt lead poisoning.

More recently, medical scientists have shown that important neurochemical changes are induced by lead in much smaller amounts than those generally associated with clinical symptoms of lead poisoning. Finally, there is considerable epidemiological evidence that low-level exposure can result in altered behavior, including attentional disorders,

¹⁸For a recent comprehensive review of the adverse health effects of lead, see ref. 47.

learning disabilities, or emotional disorders that impair classroom performance.

For these reasons, an analysis of the health costs attributable to excessive lead exposure during childhood must recognize at least three categories of costs:

- direct medical care expenditures, including hospitalization, doctors' fees, drugs, and convalescent care for preschool children who have been diagnosed as being at risk with respect to lead absorption;
- special education or institutionalization costs, or both, for school-age children who suffer permanent neuropsychological effects from exposure to lead; and
- costs to society in terms of reduced production and tax contributions from adult members of the labor force who have permanent impairments stemming from excessive exposure to lead during childhood.

Calculating health costs of lead exposure involves multiplying estimates of the number of preschool, school-age, and adult individuals with lead-induced health and intelligence deficits by cost factors that represent the opportunity costs to avoid or correct those deficits (34). Two recent analyses of regulatory proposals to reduce human exposures to lead used this approach.

In a cost-benefit analysis of options for removing lead additives from gasoline, one study (39) estimated the reduction in the number of children who would have elevated levels of lead in their blood (defined in this study as more than 25 grams per deciliter) as a consequence of removing lead from gasoline.¹⁹ The study assumed that 20 percent of all children with elevated levels would be affected severely enough to warrant compensatory education for up to 3 years. Other studies suggest that the cognitive effects and lead-induced behavioral problems may persist for at least 3 years (9,10). In the valuation step, the number of person-years in compensatory education was multiplied by an estimate of the additional costs of providing part-time special education to a child for 1 year. These estimates are presented in table 8-7. The benefits of

reducing lead in gasoline continue to increase for a number of years, as the use of leaded gasoline is gradually phased out. As the table indicates, the total health benefits of reducing the neurotoxic effects of lead on U.S. children was estimated to total more than \$500 million annually between 1986 and 1988. If adult exposure to lead, including workers' exposure, were included, the benefits would be considerably greater.

Another study developed similar estimates of the savings in medical care and compensatory education costs that would occur in a single year as a consequence of reducing the maximum contaminant level for lead in drinking water from 50 to 20 grams per liter (23). The health benefits estimate for this one-time reduction were \$81.2 and \$27.6 million (in 1985 dollars) for compensatory education and medical care costs, respectively.

SUMMARY AND CONCLUSIONS

Regulating neurotoxic substances involves consideration of both the economic benefits of using these substances and their actual or potential risks to human health and the environment. The problem of balancing benefits, risks, and the costs of regulation is not unique to the control of neurotoxic substances; it arises in all forms of health, safety, and environmental regulation. Regulations that are designed to reduce or prevent neurotoxic risks can benefit society through improvements in public health and environmental amenities. In most cases, however, society incurs costs to achieve these regulatory ends. The costs of complying with health and safety regulations may also result in increases in market prices, reductions in industry profits, and declines in new product innovation.

Many of the key Federal laws under which neurotoxic substances are regulated require agencies to ascertain the positive and negative economic consequences of regulation. In implementing these laws, Congress has generally intended that agencies prepare regulatory analyses and document the balancing of benefits, costs, and risks of proposed alternatives.

¹⁹In order to estimate the health benefits of controlling neurotoxic substances, it is important to have good data on the extent to which human populations are exposed, as well as epidemiological data that link exposures to adverse health effects. Estimates of the benefits of reducing human exposures to lead were greatly facilitated by the availability of national estimates of the prevalence of lead exposure obtained through the National Health and Nutrition Examination Survey (NHANES-II) (2).

Table 8-7-Estimates of the Health Benefits of Reducing the Neurotoxic Effects of Lead in Children
(millions of 1983 dollars)

Service	Savings					
	1985	1986	1987	1988	1989	1990
Compensatory education	\$187	\$447	\$408	\$374	\$338	\$309
Medical care	65	155	141	130	117	107
Total	252	602	549	504	455	416

SOURCE: J. Schwartz et al., *Costs and Benefits of Reducing Lead in Gasoline: Final Regulatory Impact Analysis*, EPA-230-05-85-006 (Washington, DC: U.S. Environmental Protection Agency, 1985).

In addition to these legislative provisions, the executive branch, through the Office of Management and Budget, has also mandated that agencies conduct regulatory impact analyses for regulations that may have major effects on the economy. The current OMB requirement, which has evolved through a series of executive orders, specifies that agencies must conduct benefit-cost evaluations for any regulatory proposal that is likely to have an annual effect on the economy of \$100 million or more.

To date, only a small number of regulatory actions, and hence a small number of regulatory analyses, have been directed at reducing the risks of neurotoxicity. Most of these actions have been taken to control environmental and occupational exposures to lead. Regulatory impact analyses of regulations to reduce the amounts of lead in gasoline and in drinking water provide some of the best examples to date of assessments of the economic consequence of controlling neurotoxic risks.

Analyzing the economic consequences of controlling neurotoxic risks is a two-step process. The first step, risk assessment, involves using data from epidemiological, toxicological, and other studies to estimate the health and environmental risks associated with various levels of exposure to the substance in question. The second step involves making estimates of the costs, benefits, and other economic impacts associated with achieving a specific level of risk reduction.

One economic issue that has emerged in regulating neurotoxic substances concerns the costs of screening and testing these substances for their neurotoxic hazard potential. Experience with neurotoxicity testing is still relatively limited, creating uncertainty regarding the available cost estimates for this type of testing. Because of the uncertainty regarding these costs, OTA obtained estimates of the costs of several types of neurotoxicity tests from a

number of individuals in government, industry, and academia.

Cost estimates were obtained for standard acute, subchronic, and chronic toxicity test protocols augmented with four neurological evaluations: functional observational battery, motor activity, neuropathology, and schedule-controlled operant behavior. The median estimates derived from OTA's survey indicate that a complete set of core neurotoxicity tests, including a functional observational battery, motor activity, and neuropathology, may add from 40 to 240 percent to the costs of conventional toxicity tests currently required by EPA. By far the largest portion of the added cost comes from the addition of neuropathology evaluations, which are needed to determine whether structural change in the nervous system has occurred and the nature and significance of the change. Based on its survey, OTA found that acute neurotoxicity tests (including EPA's functional observational battery, motor activity test, and neuropathology evaluations) may add about \$50,000 to the cost of standard acute toxicity tests. Subchronic neurotoxicity tests may add \$80,000, and chronic tests may add about \$113,000. The EPA subchronic schedule-controlled operant behavior test may add about \$64,000. However, the functional observational battery alone would add only \$2,500 to the cost of conventional acute toxicity test. A conventional acute test involving oral exposure costs about \$21,000.

Testing costs should be viewed in the context of the total cost to industry of marketing a new product, potential profits resulting from the sale of the product, the impact of initially high test costs on the innovation process, and the health benefits of minimizing public exposure to neurotoxic substances.

For the development of new drugs and pesticides, which have development times of 8 to 10 years and development costs of \$50 million to \$100 million or

more, the costs of additional neurotoxicity testing are very small. For industrial chemicals with specialty uses, on the other hand, additional neurotoxicity testing could add substantially to costs of tests that are currently done and could lead to a reduction in the innovation of certain classes of low-volume products.

The benefits of regulating neurotoxic substances can be measured in terms of the human and monetary values placed on reduction of risk. A number of approaches have been used to assign monetary values to reducing the risks of mortality, morbidity, and disability. Lead has been the subject of an in-depth economic analysis. A 1985 study estimated that the total health benefits of reducing the neurotoxic effects of lead on U.S. children would be more than \$500 million annually between 1986 and 1988. If adult exposure to lead, including workers' exposure, were included, the benefits would be considerably larger.

Although the health and economic benefits of limiting public exposure to neurotoxic substances are more difficult to estimate than the costs of regulation, the example of lead illustrates the importance of considering the potentially large monetary benefits of regulatory actions. Like other toxicity testing, neurotoxicity testing is conducted to prevent adverse health effects; hence, the benefits of such testing may not be readily apparent and may accrue well into the future. Often, the immediate costs of testing receive considerable attention, but the sizable potential benefits of preventing public exposure to a hazardous substance receive comparatively little attention.

As indicated earlier, neurotoxic substances, in particular abused drugs, play a significant, causal role in the development of neurological and psychiatric disorders; however, the precise extent of the contribution remains unclear. Mental disorders and diseases of the nervous system contribute substantially to health costs in the United States. In 1980, they ranked as the third and fifth most expensive medical conditions in terms of personal health-care expenditures (see table 1-3 in ch. 1). The estimate of nearly \$40 billion (1980 dollars) does not include values for the lost productivity, restricted activity, and other social costs that frequently accompany mental illness or other forms of mental impairment.

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