

WORKSHOP OVERVIEW

EPA's Neurotoxicity Risk Assessment Guidelines^{1,2}

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The proposed Neurotoxicity Risk Assessment Guidelines (U.S. EPA, 1995c *Fed. Reg.* 60(192), 52032-52056) of the U.S. Environmental Protection Agency (EPA) were the subject of a workshop at the 1997 Meeting of the Society of Toxicology. The workshop considered the role of guidelines in the risk assessment process, the primary features, scientific basis, and implications of the guidelines for EPA program offices, as well as for industrial neurotoxicologists from the perspectives of both pesticides and toxic substances regulation. The U.S. National Academy of Sciences (NAS, 1983, Risk Assessment in the Federal Government: Managing the Process) established a framework for distinguishing risk management from risk assessment, the latter being the result of integrating hazard identification, hazard characterization, and exposure assessment data. The guidelines are intended to establish operating principles that will be used when examining data in a risk assessment context. The proposed neurotoxicity risk assessment guidelines provide a conceptual framework for deciding whether or not a chemically induced effect can be considered to be evidence of neurotoxicity. Topics in the proposed guidelines include structural and functional effects, dose-response and -duration considerations, and relationships between effects. Among the issues that must be considered are the multiplicity of chemical effects, the levels of biological organization in the nervous system, and the

tests, measurements, and protocols used. Judgment of the adversity of an effect depends heavily on the amount and types of data available. The attribution of a chemically induced effect to an action on the nervous system depends on several factors such as the quality of the study, the nature of the outcome, dose-response and time-response relationships, and the possible involvement of nonneural factors. The guidelines will also serve as a reference for those conducting neurotoxicity testing, as well as establish a consistent approach to neurotoxicity risk assessment by regulators. Extending this approach through international harmonization would be advantageous to the development of products for a worldwide market. Thus, both risk assessors and regulated industries have a large stake in the guidelines to provide a framework that will lead to accurate risk assessment decisions. © 1997 Society of Toxicology.

A workshop entitled EPA's Neurotoxicity Risk Assessment Guidelines was held at the 36th Annual Meeting of the Society of Toxicology (SOT) in Cincinnati, Ohio, in 1997, which was jointly sponsored by the Neurotoxicology and Risk Assessment Speciality Sections of the SOT. The U.S. Environmental Protection Agency (EPA) published Proposed Guidelines for Neurotoxicity Risk Assessment for public comment (EPA, 1995c). When final, these guidelines will provide the scientific basis that the EPA will use to make regulatory decisions based on neurotoxicity data. Because the manner in which the EPA interprets data on neurotoxicity could affect many members of the SOT, the workshop was held to discuss the role, composition, and implications of the proposed guidelines.

The overall goals of the workshop were: (1) to provide an overview of the role risk assessment guidelines play in the risk assessment process; (2) to present the major features and scientific basis of the proposed guidelines; and (3) to discuss the unique perspectives of some of the major parties potentially influenced by the guidelines, including EPA program offices and regulated industries. Topics included risk

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assessment principles and guidelines, the scientific basis of the EPA's Neurotoxicity Risk Assessment Guidelines, how the guidelines will be used by the EPA's Program Offices, and the implications of the guidelines for industrial neurotoxicologists from the perspectives of those regulated under both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA).

RISK ASSESSMENT AND THE ROLE OF RISK ASSESSMENT GUIDELINES

(Michael L. Dourson and Jacqueline Patterson)

The practice and science of risk assessment in the U.S. was propelled forward by the National Academy of Sciences' (NAS) 1983 publication *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983). In this publication, commonly referred to as "the Red Book," the NAS outlined a paradigm with four distinct steps to the risk assessment process: hazard identification, dose-response assessment, exposure assessment, and risk characterization. Risk management used the results summarized in the risk characterization step to make decisions incorporating other factors, including economics, technology, and public policy. The EPA adopted many of the NAS recommendations and institutionalized the risk assessment/risk management process throughout the Agency.

Before the NAS paradigm, risk assessment activities of the various EPA offices followed the procedures and practices of each office, sometimes leading to inconsistent conclusions. The distinction between the scientific judgments of risk assessment and the policy decisions of risk management was frequently not made clear. In addition, without clearly written documentation for the approaches used, those outside the process were not always able to understand the basis for the results. With the NAS publication, the EPA adopted the document's definitions and framework and began in earnest a process to make its risk assessment practices consistent across the Agency. Procedures for assessing risk for a number of endpoints were published in five risk assessment guidelines in 1986 in the areas of carcinogenicity, mutagenicity, exposure assessment, chemical mixtures, and developmental toxicity (EPA, 1987).

This first group of guidelines has been enhanced with the development of guidelines for reproductive toxicity (EPA, 1994a), revised guidelines for developmental toxicity (EPA, 1991b), exposure assessment (EPA, 1992), and carcinogenicity (EPA, 1996). The Agency is also working on revisions to the chemical mixtures guidelines. Current efforts to finalize the Neurotoxicity Risk Assessment Guidelines (EPA, 1995c) are the subject of this workshop. Although Agency efforts to develop systemic toxicity guidelines in the 1980s were never completed, a number of papers have been pub-

lished on related topics, including reference dose (RfD) (Barnes and Dourson, 1988; Dourson, 1994), reference concentration (RfC) (EPA, 1994b; Jarabek, 1994), and benchmark dose (EPA, 1995a; Barnes *et al.*, 1995). Guidance is also available on risk characterization (EPA, 1995b).

The objective of the EPA's risk assessment guidelines is to provide guidance for evaluating risk to humans from exposure to chemicals. Specifically, each set of guidelines provides definitions for terms, rationales for approaches to evaluating animal and human data, and overall consistency across the different endpoints in appropriate areas. These documents, and the publications on RfD, RfC, and benchmark dose, also guide judgments on whether effects are adaptive, compensatory, or adverse. Interpretation of effects or a syndrome of effects as the critical effect is also discussed. Techniques for dose-response extrapolation are described. The EPA has been the world leader in developing guidelines and publishing them for both internal and external use.

An additional role for risk assessment guidelines is to serve as a framework in which to identify the need for further research and its resulting potential for reduction of uncertainty. These guidelines are not static; they were designed to be changed as the science evolves. The EPA's revisions to the developmental toxicity, carcinogenicity, and exposure guidelines demonstrate this clearly.

An additional EPA effort to enhance consistency in risk assessment activities across the Agency was the creation of an internal peer review process to review the results of its program-specific dose-response assessment deliberations. The resulting consensus opinion of these work groups is then made available to the public through the Integrated Risk Information System (IRIS). IRIS has been one of the most successful risk assessment resources ever developed. Its risk assessment values are used by public and private entities around the world in their efforts to determine the human health impacts from chemical exposures.

Within the guideline's development activities, the EPA has had the opportunity to define areas of scientific uncertainty where further research can assist in reducing that uncertainty. Several hundred publications on a variety of topics related to hazard identification, dose-response assessment, and exposure assessment techniques have been published by the EPA alone, with many additional publications by others in the field. The EPA's Office of Research and Development recently restructured its office and research activities to address directly the risk assessment paradigm.

In summary, the 1983 NAS publication illuminated the role of risk assessment and risk management, clearly distinguishing the two. This publication led to the development of risk assessment guidelines within the EPA which ensured consistency across the Agency, and provided others the abil-

ity to understand and evaluate the Agency's efforts within a common framework. Development of these guidelines has allowed risk assessors to utilize better the scientific information available in particular disciplines, such as neurotoxicology, and demonstrated how laboratory research can be used in this important area. Additional research has focused on areas which can reduce uncertainty in assessments and these improvements have been used to update existing guidelines.

NEUROTOXICITY RISK ASSESSMENT GUIDELINES AND THEIR SCIENTIFIC BASIS (Hugh A. Tilson)

The Proposed Neurotoxicity Risk Assessment Guidelines (EPA, 1995c), are intended to facilitate the assessment by Agency personnel of agents that are suspected to cause neurotoxicity in accordance with the policies and procedures established in the statutes by the EPA. The guidelines were developed under the auspices of the Risk Assessment Forum by a work group composed of scientists from throughout the Agency. Selected drafts of the guidelines were peer-reviewed internally and by experts from universities, environmental groups, industry, and other governmental agencies. A earlier draft underwent peer-review in a workshop held in June, 1992, and was subsequently reviewed internally by the Concordance and Oversight Committees of the Risk Assessment Forum. The Committee on the Environment and Natural Resources of the Office and Science Technology Policy and the Science Advisory Board of the EPA also reviewed the guidelines in August 1995, and July 1996, respectively.

The guidelines describe several default assumptions to be used in the risk assessment process as discussed in the National Research Council report on science and judgement in risk assessment (NRC, 1994). Several assumptions concerning animal-to-human extrapolation and the presence of a threshold for neurotoxic effects are discussed. The guidelines also contain a number of working definitions of specific terms related to neurotoxicology, as well as a discussion concerning crucial concepts related to reversible and irreversible effects, direct and indirect effects, and reserve capacity of the nervous system. The guidelines define the steps involved in hazard identification to make a qualitative decision concerning whether a chemical has neurotoxic potential. The section on dose-response assessment defines the quantitative relationship between dose and effect. The guidelines also provide guidance on exposure assessment, which provides an estimate of human exposure levels for particular populations from all potential sources. The risk characterization section of the guidelines combines the hazard identification, dose-response assessment, and exposure assessment components to estimate some measure of the risk for neuro-

toxicity. As part of the risk characterization, a summary of the strengths and weaknesses of each component of the risk assessment is given along with major assumptions, scientific judgments and, to the extent possible, qualitative and quantitative estimates of the uncertainties related to determining a RfD or RfC.

The draft neurotoxicity risk assessment guidelines requested public comment on several special issues, including (1) the issue of compensation and recovery of function in neurotoxicological studies and how to account for compensation in neurotoxicology risk assessment; (2) the use of blood and/or brain acetylcholinesterase activity as an indication of neurotoxicity for risk assessment; (3) endpoints indicative of neurotoxicity that may not be covered by the guidelines, i.e., endocrine-disruption or neuroendocrine-mediated neurotoxicity; and (4) the possibility of no threshold for some neurotoxic agents. The Agency received responses from 25 separate groups or individuals, including chemical companies and/or trade associations (7), environmental advocacy groups (2), an animal rights advocacy group (1), governmental agencies (7), individuals in academia or private medical practice (4), and individual or corporate consultants or lobbyists for not-for-profit institutions (4).

The guidelines stressed that the risk assessor should note that reversible neurotoxic changes should be of concern because the nervous system, particularly cells in the central nervous system, have a limited capacity for regeneration and that the nervous system has the capacity to compensate for damage up to a certain point. Therefore, reversibility of effects may be indicative of this compensatory response or represent an activation of repair capacity, which could decrease future potential adaptability. Public comment indicated general support for the discussion concerning compensation and reversible effects in the guidelines. It was indicated, however, that the concept of reserve capacity should be included in the guidelines to help risk assessors understand the possible implications of reversible neurotoxic effects. Behavioral and neurological functioning can be viewed as an adaptive process operating within some upper and lower limits, i.e., the functional reserve. Exposure to a neurotoxicant alters the dynamic equilibrium of the organism's functioning, which up to some point is maintained within a normal range by extant compensatory mechanisms. If it is assumed that a finite capability is built into the system, at some point during exposure the reserve capacity of the system will be depleted and function will deteriorate (Tilson and Mitchell, 1983).

Considerable questions have arisen within the EPA and elsewhere as to whether inhibition of cholinesterase activity constitutes an adverse effect for defining hazard potential and evaluating risk. The neurotoxicity risk assessment guidelines indicated that there is general agreement that clinical signs

of cholinesterase inhibition could be used for risk assessment. In addition, although a reduction of brain cholinesterase activity may or may not be accompanied by clinical signs, significant reductions in brain cholinesterase are themselves toxic or would lead to a neurotoxic effect if exposure were to persist over time or increase in magnitude. The guidelines also indicated that inhibition of red blood cell and/or plasma cholinesterase may or may not be accompanied by clinical manifestations and that inhibition of blood indicators of acetylcholinesterase activity serve as a biomarker of exposure. There was strong public support for the guidance concerning chemical-induced inhibition of acetylcholinesterase, although some suggested that a threshold of inhibition, e.g., 20%, be used rather than a statistically significant effect.

The neurotoxicity risk assessment document contains considerable guidance concerning procedures to assess chemical-induced behavioral, neurochemical, neurophysiological, and neuropathological changes in the nervous system of humans and animals. The public comment indicated that, in general, the risk assessment guidelines were thorough and adequate. There was a consensus that the document did not need to be modified to include guidance for the assessment of chemicals that affect the neuroendocrine or reproductive systems since the methods described in the document would be sufficient to detect chemical-induced changes in these systems. There was, however, general support for adding background information concerning basic neuroendocrinology and the need to correct details concerning certain endpoints (i.e., NTE, GFAP) and/or expand the description of certain sections (i.e., assessment of subjective effects in humans, brain imaging, motor activity, schedule-controlled behavior).

Like other noncancer endpoints, the neurotoxicity risk assessment guidelines assume that there is a threshold effect of chemicals on the nervous system. Although there is some indication that a threshold may not exist for developmental exposure to some chemicals such as lead or methyl mercury, there was overwhelming public support for the concept of a threshold for neurotoxicity risk assessment. Another viewpoint expressed was that although there may be a threshold for neurotoxic effects, they are often difficult to determine empirically. Therefore, it would be more precise to assume that, like other noncancer endpoints, there is a nonlinear dose-response relationship for neurotoxicants.

Public comment was also received on a wide range of other topics. One issue of considerable interest concerned the use of quantitative approaches other than the LOAEL/NOAEL procedure for determining the reference dose or concentration. The guidelines discuss the limitations of the LOAEL/NOAEL approach and encourage the calculation of the benchmark dose (BMD) for neurotoxicity and other health effect endpoints. Public comment supported the EPA

for exploring other quantitative models for risk assessment, but most commentators were concerned that the BMD was not ready for use in neurotoxicity risk assessment. Others indicated that if the use of the BMD were encouraged, then there was a need to include caveats for using the BMD in the manner that was used for the NOAEL/LOAEL approach.

The Science Advisory Board (SAB) of the EPA reviewed the neurotoxicity risk assessment guidelines in July 1996. The SAB identified many of the same issues raised during the public comment period. Once the SAB issues a final report, the guidelines will be revised in accordance with their recommendations and published in final form.

AN EPA PROGRAM OFFICE PERSPECTIVE ON
NEUROTOXICITY RISK ASSESSMENT
(W. F. Sette and R. C. MacPhail)

In the EPA, the Office of Pesticide Programs (OPP), and its sister Office of Pollution Prevention and Toxic Substances (OPPT), are responsible for implementing the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), whose focus is the registration and regulation of pesticides, and the Toxic Substances Control Act (TSCA), whose focus is industrial chemicals. Risk assessments under both TSCA and FIFRA focus on determinations of "unreasonable risk of adverse effects on human health or the environment."

The Health Effects Division of OPP is responsible for reviewing all of the animal and human toxicology data used to support a pesticide's registration. It is also responsible for performing risk assessments for potential health effects. These risk assessments are typically derived from reference doses (RfDs) for chronic dietary exposures or short-term exposure limits for acute dietary exposures, and short-term dermal and/or inhalation occupational and residential exposures. There are currently two committees that meet weekly to perform quality control assessments of the study reviews on a particular pesticide and to establish the chronic reference doses and/or other exposure limits. Review of any neurotoxicity studies and other studies that include data related to neurotoxicity is one area considered in these deliberations.

Two critical steps in neurotoxicity risk assessments in OPP, then, are judging adversity and ascribing adverse chemical-induced effects to neurotoxicity. These judgments may vary as a function of the amount and types of data available.

Neurotoxicity may be simply defined as any adverse effect on the structure or function of the nervous system (EPA, 1991a). In contrast, consider the criteria for identification of a human neurotoxicant provided by Spencer and Schaumburg (1985): "1) a consistent pattern of neurological dysfunction in humans; 2) comparable dysfunction in animals; and 3) reproducible lesions in animals and humans which

are related to the neurobehavioral dysfunction expressed.' The degree to which a chemical's database satisfies these criteria may be evaluated in terms of several types of validity. The concept of validity has been adapted from the literature on human psychological testing, where it has long been used to evaluate different tests of intelligence or other abilities and aptitudes (Sette, 1987). There are five principal questions raised in the criteria and definition that may be described in terms of four types of validity: the extent to which effects can be viewed as consequences of exposure (content validity); the correlation between measures of behavior, physiology, biochemistry, and morphology (concurrent validity); whether effects in animal models are predictive of what will happen in humans (predictive validity); whether the effects are adverse or toxicologically significant (construct validity); and whether the effects are neurotoxic (construct validity). The definition is focused on judgments of a single effect. It is simple, perhaps deceptively so, and dependent on how one defines adverse, a question of construct validity. Describing the criteria in terms of validity, a consistent pattern of neurological dysfunction should provide concurrent validity in terms of the pattern and reliability of effects, and construct validity to the extent that the tests identify neurological dysfunctions. Comparable effects in animals involve predictive validity between species and content validity in that the animal models often establish a much clearer relation between exposures and effects. Lesions related to the dysfunctions involve concurrent validity between dysfunctions at different levels of biological organization. While the first definition may be satisfied by a change in a single endpoint, satisfaction of the general criteria for a human neurotoxicant would require considerable data. In OPP, despite all of the animal studies that are often required for pesticides, the availability of sufficient data to satisfy all these criteria is rare.

Adversity may be defined as "alterations from baseline that diminish an organism's ability to survive, reproduce, or adapt to the environment" (EPA, 1995c). This third element, adaptation to the environment, places emphasis on functional deficits that are largely reflected as changes in behavior, but other types of effects, e.g., neurophysiological habituation, may also reflect adaptations. Some judgment is also required regarding the degree of any alteration that may be deemed significant. Adversity also has subjective psychological elements in that people's views of the adversity of effects may depend on their nature, the exposure situation (Slovic, 1987), and how the risk assessment is framed (Tversky and Kahneman, 1981). There will always be tension between broad social views of what is adverse and the more rigorous demands of sound scientific conclusions about whether a chemical is a human neurotoxicant. (See also *Ann. Am. Acad. Political Social Sci.*, May 1996).

There are some differences between the types of data in making judgments regarding both adversity and neurotoxicity (Sette and MacPhail, 1992). In general, histopathological effects are measures of the physical integrity of the nervous system. These types of effects have been historically regarded as adverse. But such damage may occur in the absence of any demonstrable functional consequences. Neurophysiological effects and neurochemical effects are also, for the most part, reflections of a chemical's action on the nervous system, but judgement to their adversity is more dependent on their plausible relation to functional consequences, e.g., EEG changes and seizures, or cholinesterase inhibition and blurred vision. Behavioral changes are generally considered adverse (at some degree of change) in that they are altered responses to the environment, but their relation to the nervous system is often much less clear, and so their construct validity as evidence of neurotoxicity is generally less certain. Factors important to judging the neurotoxicity of behavioral effects include functional domains (concurrent changes in multiple related endpoints) or physiological constructs, correlative neurophysiological, neurochemical, or neuropathological effects, dose-response and time-dependent relations, and concurrent systemic toxicity. However, the relationship between systemic organ toxicity and behavior is generally not clear nor as well studied as the relationship between behavior and the nervous system.

In summary, the interpretation of data typically gathered in neurotoxicity studies can be viewed as judgments of their adversity and neurotoxicity. Adversity is defined in broad functional terms and depends, in part, on psychological perceptions, the framing of the questions, and social values. Neuropathological effects are most clearly neurotoxic and generally seen as adverse, although the functional consequences may be unclear. Neurophysiological and neurochemical effects are generally considered neurotoxic, but their adversity depends more on their empirical or presumptive functional consequences. Behavioral effects are generally adverse, but their reflection of neurotoxicity is less clear and depends on a variety of constructs and other measures.

**A FIFRA-REGULATED INDUSTRIAL PERSPECTIVE OF
THE EPA'S DRAFT NEUROTOXICITY RISK
ASSESSMENT GUIDELINES
(Abby A. Li)**

Neurotoxicity risk assessment has become a driving force for regulatory actions and clean-up decisions. The TSCA Multi-substance Test Rule of Neurotoxicity (TSCA; 40 CFR Part 799, July 27, 1993); the increasing number of data calls for neurotoxicity testing under FIFRA, and the recent inclusion of carbamates on the Resource Conservation and Recovery Act (RCRA) hazardous waste lists (60 FR 7824,

Feb. 9, 1995) are a few examples of recent regulatory decisions that are dependent upon neurotoxicity risk assessment.

The publication of the proposed U.S. EPA's Neurotoxicity Risk Assessment Guideline is a very important step forward in making this risk assessment more consistent, transparent, and science based. Dr. Hugh Tilson and the many other authors at the EPA have done an outstanding job developing a guideline that provides a comprehensive understanding of many areas of neurotoxicology as well as practical and useful guidance for those conducting and assessing studies for regulatory purposes.

The purpose of the neurotoxicity risk assessment guidelines is to protect humans from developing neurotoxic diseases as a result of exposure to chemicals. Our success in achieving this goal will depend, in part, upon the accuracy with which we define neurotoxic effects. In our eagerness to protect the public and environment, the temptation is to cover all the bases by defining any change that can possibly be linked to the nervous system as a neurotoxic effect, including those that we do not fully understand and, hence, are most fearful of missing. While some degree of conservatism is necessary to compensate for gaps in scientific understanding, an overly conservative definition of neurotoxicity can have the harmful effect of focusing resources on issues that have little impact on reducing risk.

Neurotoxicity risk assessment is uniquely challenging because of the large contribution of functional and behavioral measures. While inclusion of these measures elevate the importance of functional behavioral changes, the potential danger is that all changes in behavior and function automatically will be viewed as neurotoxic effects. This is particularly problematic because studies must be conducted at the maximum tolerated doses (MTD), which is a dose level that is often orders of magnitude above expected exposure levels. At sufficiently high dose levels, all materials will produce functional effects, many of which are likely to be nonspecific indicators of general intoxication and not neurotoxicity. The risk assessment process already allows us to protect against these effects without having to classify them as neurotoxic effects. Classifying effects as neurotoxic can lead to regulatory enforcement actions (such as RCRA waste lists) some of which do not take exposure levels into account. These regulatory actions are better directed toward direct-acting neurotoxicants. Also, indiscriminately classifying adverse effects on function as neurotoxic can compromise effective hazard communication to the public.

Thus, it is important that risk assessors receive balanced guidance that will allow us to distinguish chemicals acting directly on the nervous system from those that produce effects indirectly. The right balance can be achieved by making the entire Neurotoxicity Risk Assessment Guideline consistent with two very important principles outlined in EPA's definition of neurotoxic effect.

EPA states, "Neurotoxicity is an adverse change in the structure or function of the central and/or peripheral nervous system following exposure to a chemical, physical, or biological agent. . . . Changes in function can also result from toxicity to other specific organ systems, and these indirect changes may be considered adverse but not necessarily neurotoxic" (FR 60:52035).

The first principle is that neurotoxicity is an adverse effect, not just any change. The second principle implies that changes in function can also result from toxicity to other specific organ systems, and these indirect changes may be considered adverse but not necessarily neurotoxic. The EPA's neurotoxicity risk assessment guidelines can be improved if all the sections discussing specific neurotoxic endpoints are made consistent with these two principles. There are some sections that are consistent, but several that are not. Let me illustrate with examples using endpoints such as motor activity and learning and memory which are intuitively more familiar to most people.

The section discussing motor activity states that "neurotoxic agents generally decrease motor activity (FR 60: 52045)" but does not balance this statement by also stating that many agents that are not specific neurotoxicants also cause decreases in motor activity at higher doses. Without this clarification, the reader could be left with the incorrect impression that any decrease in motor activity is evidence of neurotoxicity. A simple clarification will make this section consistent with the EPA's definition of neurotoxicity.

This section on motor activity does discuss different levels of concern. "Agent-induced changes in motor activity associated with other overt signs of toxicity (e.g., loss of body weight, systemic toxicity) or occurring in non-dose-related fashion are of less concern than changes that are dose dependent, related to structural or other functional changes in the nervous system, or occur in the absence of life-threatening toxicity (FR 60: 52045)." However, guidance on how these different levels of concern will actually translate into a meaningful difference in the final risk assessment process is needed. As written now, changes of lesser and greater concern are both considered neurotoxic effects and will be treated identically to those of lesser concern in the final risk assessment process.

The example with motor activity illustrates the importance of adhering to the principle outlined by the EPA's definition of neurotoxicity that changes in function can be adverse but are not necessarily neurotoxic. The second principle is that neurotoxicity is an adverse effect, not just any change from baseline. An adverse effect was defined by the EPA as a change from baseline that diminishes an organism's ability to survive, reproduce, or adapt to the environment. We have the ability to measure both enhancements and deficits in many functions and behaviors. For example we can measure

enhancements in cognition. Yet the guidelines appear to imply that all changes in learning and memory are adverse. In other words, improvement in learning or memory could be considered a neurotoxic effect. Likewise, improved performance on an operant task which leads to more food reinforcement and hence an improvement in the animal's ability to adapt to the environment would also be a neurotoxic effect. Yet these effects do not fit EPA's definition of an adverse effect. If the concern is that improvement in learning and memory or performance of a complex behavior may indicate that the chemical is acting centrally to produce other unknown adverse effects in the central nervous system, then this should be stated as a default assumption based on science policy and not presented as if it were objective scientific fact. It would be misleading to conclude that this chemical produces adverse effects on learning and memory.

Some of the previous speakers introduced a new definition of an adverse effect that was not in the draft EPA Neurotoxicity Risk Assessment Guidelines; namely, an "unwanted effect." This definition should not be included in these guidelines. It is inconsistent with the EPA's Office of Pesticide Program (OPP) guidance on risk assessments, which states that "risk assessments should be transparent, in that the conclusions drawn from the science are identified separately from policy judgments, and the use of default values or methods and the use of assumptions in the risk assessment are clearly articulated (EPA, 1995e). Defining an adverse effect as an "unwanted effect" will encourage interpretations that are no longer scientifically objective or rigorous and hopelessly intertwined with policy decisions.

Adhering to the EPA's balanced definition of neurotoxicity is especially important in light of the EPA's discussion on characterizing the sufficiency of evidence for neurotoxic effects. At present, the guidelines are written in a way that makes it very difficult to provide any reasonable certainty of no harm: According to the guidelines, a series of negative standard toxicity studies are not sufficient evidence of "no harm" to the nervous system. Negative screening studies that may measure general functional endpoints are not sufficient evidence of no harm for other specific neurotoxic effects such as cognition. This guidance dismisses a large body of potentially valuable data that should enter into the risk assessment evaluation, and it also ignores the value of a tiered approach to neurotoxicity testing.

In summary, the draft EPA's Neurotoxicity Risk Assessment Guidelines is an important step forward in making sure that there is a consistent approach to neurotoxicity risk assessment. This will be very beneficial to the registration and review process of chemicals. Effective protection of the public will depend, in part, upon the ability to discriminate between indirect and direct adverse effects on the nervous system. The EPA's definition of neurotoxicity and adverse

effects that was in the draft guideline provides a good guidance on how to distinguish between indirect and direct effects. The EPA's definition of a neurotoxic or adverse effect should encourage scientifically objective interpretation of the data and should not be corrupted by the ill-defined concept of "unwanted" effects. Guidance should be included as to how different levels of concern will make a difference in the risk assessment process. Finally, sufficient evidence of "reasonable certainty of no harm" should be defined in a manner that acknowledges the value of a tiered approach to neurotoxicity testing and of the value of well-conducted standard toxicity studies.

IMPLICATIONS OF THE EPA'S NEUROTOXICITY RISK ASSESSMENT GUIDELINES FROM A TSCA-REGULATED INDUSTRIAL PERSPECTIVE

(John L. O'Donoghue)

The Toxic Substances Control Act (TSCA) regulates the import, export, production, use, and disposal of nearly every product and synthetic or processed natural chemical present within the United States. These include household products, consumer products, bulk industrial chemicals, and chemical intermediates, including site-limited intermediates. Even though pesticides, pharmaceuticals, food and feed additives, and other regulated products are not considered TSCA-regulated materials, their ingredients, processing, or process waste may be regulated under TSCA. Thus, the EPA's Neurotoxicity Risk Assessment Guidelines will have a very broad impact not only on TSCA-regulated companies, but also on a wide range of other commercial enterprises and the American consumer.

The publication of the final Neurotoxicity Risk Assessment Guidelines will knit together a series of other guidelines and processes that have been developed to detect and assess potentially neurotoxic substances. The various parts of the overall neurotoxicity risk assessment process includes good laboratory practice guidelines, systemic toxicity test guidelines, neurotoxicity test guidelines, and neurotoxicity risk assessment methods such as the safety factor and the bench-mark dose (BMD) methods for calculating risk levels. The Neurotoxicity Risk Assessment Guidelines deal with each of these other processes and how they relate to each other, and provide information on how to handle and interpret data from various sources to a risk assessor.

The primary target audience for the Neurotoxicity Risk Assessment Guidelines are EPA risk assessors and EPA contractors conducting risk assessments. The individuals using the Neurotoxicity Risk Assessment Guidelines in most instances will not be neurotoxicologists, but rather individuals with expertise in general principles of toxicology and risk assessment. The absence of a neurotoxicologist in the risk

assessment process is of concern to TSCA-regulated companies. However, since many risk assessments on TSCA-related materials are currently being performed by individuals without specialist training in neurotoxicology, the availability of a published, widely reviewed Neurotoxicity Risk Assessment Guidelines should be seen as a significant improvement in the overall process. Publication of the Neurotoxicity Risk Assessment Guidelines could be looked upon as an internal EPA harmonization process for risk assessment methodology. The Neurotoxicity Risk Assessment Guidelines can be expected to make neurotoxicity risk assessments more consistent across the various EPA program offices dealing with TSCA-related issues.

While the Neurotoxicity Risk Assessment Guidelines are intended to be used by EPA risk assessors, it is abundantly clear that they set a standard for neurotoxicity risk assessment for others as well. In addition to the use envisioned by the EPA, TSCA-related companies are likely to use the guidelines while working on pollution-prevention activities. Such use, however, will require a flexible interpretation of the guidelines. A literal interpretation of the Neurotoxicity Risk Assessment Guidelines would lead a risk assessor to use the guidelines as an "end of pipe approach," that is to say they would be used when complete data sets are available for analysis. However, decisions about which chemicals to use in manufacturing processes are made early in the product development cycle, not at the immediate premanufacturing point when regulatory clearances are sought. Many companies use product development processes that begin with a phase where products are first conceptualized. Successful concepts move on to a phase where the technology is developed to bring the concept to a manufacturable product. Only when the technology actually exists to create a product does the product development process move into high gear. Once the product development and process development needed to manufacture a product are in place, a new product can actually begin to have a marketplace presence. Company and consulting toxicologists contribute to the product development cycle at earlier time points than ever before by collecting and interpreting toxicity data to meet the high expectations of the marketplace for ever-improving products. The Neurotoxicity Risk Assessment Guidelines can play a role in company product stewardship and pollution-prevention activities by providing a guide to explain how the EPA expects neurotoxicity data to be interpreted for TSCA purposes. Early assessment of neurotoxicity data against Neurotoxicity Risk Assessment Guidelines standards means that the product development process can be adjusted to eliminate or improve the control of potentially neurotoxic substances during the product development process rather than at the end of the process when significant additional resources might be required to ensure a high level of product steward-

ship. The Neurotoxicity Risk Assessment Guidelines can be expected to assist TSCA-regulated companies and help the EPA reach goals which go beyond neurotoxicity risk assessment and have more to do with proactive pollution prevention.

A potential outcome of publication of the Neurotoxicity Risk Assessment Guidelines is that it will set a standard for development of an international or global standard for doing neurotoxicity risk assessments. Currently, there is interest around efforts to harmonize chemical classification and hazardous materials-labeling practices to replace the several, and sometimes conflicting, systems in place in the global marketplace. While the International Programme on Chemical Safety (1986) has produced a well-received environmental health criteria document on neurotoxicity assessment, the Neurotoxicity Risk Assessment Guidelines provides the first widely available process for regulatory agency use. With publication of the Neurotoxicity Risk Assessment Guidelines, the EPA will have provided a model document upon which an international or global standard can be built.

While the above aspects may be seen as improvements in the overall risk assessment process, there remain some serious concerns with the Neurotoxicity Risk Assessment Guidelines. Since these concerns have not been fully addressed during the Neurotoxicity Risk Assessment Guidelines review and comment, they bear attention during implementation of the Neurotoxicity Risk Assessment Guidelines or on a case-by-case basis during reviews on specific chemicals. A primary concern is the use of the Neurotoxicity Risk Assessment Guidelines to identify chemicals as neurotoxic. The concern about this issue has a number of different facets to it. First, there is concern that the Neurotoxicity Testing Guidelines, which will be used to collect data for assessment using the Neurotoxicity Risk Assessment Guidelines, are designed such that the tests, especially the functional observational battery (FOB), are likely to provide false-positive results. Because the Neurotoxicity Testing Guidelines include many different endpoints, the probability of an endpoint showing "an effect" is quite high. Perhaps more important is that the Neurotoxicity Testing Guidelines and other test guidelines that include behavioral endpoints are typically conducted at toxic dose levels, which can cause nonspecific behavioral manifestations that can be misinterpreted as neurotoxicity. To the EPA's credit, it has conducted research looking at such effects and the *1995 Annual Report of the National Health and Environmental Effects Research Laboratory* (EPA, 1995d) has concluded that "stress has been shown to affect the manifestations of chemical-induced neurotoxicity and can have a significant affect on quantitative and qualitative estimates of neurotoxic risks." The NHEERL annual report has also reported that "the FOB and motor activity were used in a comparative study . . . to assess the

acute and subacute effects of 10 industrial and agricultural chemicals. . . . Chemicals expected to have little or no neurotoxicity affected some behavioral measures at high doses.” While sections of the Neurotoxicity Risk Assessment Guidelines partially address the concern about nonspecific effects being used to identify materials as neurotoxic, concern remains that the Neurotoxicity Risk Assessment Guidelines will result in the incorrect identification of many chemicals as neurotoxic.

While there is obvious concern that materials may be easily and inappropriately classified as neurotoxic, there is also concern that risk assessors using the Neurotoxicity Risk Assessment Guidelines may be reluctant or unable to identify materials which should be of no concern for neurotoxicity. That is, that it may be impossible to provide enough data to demonstrate that a material does not present a risk of neurotoxicity under typical conditions of use. The Neurotoxicity Risk Assessment Guidelines provide guidance to the risk assessor on how to characterize the health-related database available for neurotoxicity risk assessment. This guidance is provided to identify chemicals with data which provide sufficient or insufficient evidence for classification as a neurotoxicant. However, well-studied chemicals that show no signs of neurotoxicity are left in regulatory limbo, not regarded as neurotoxic but never really identified as nonneurotoxic either. While it is understandable that the Agency has concerns about “the inherent difficulty in ‘proving any negative,’ ” it is not understandable why it has not created a classification category identified as “chemicals of low concern for neurotoxicity.” If the Agency agrees that its test guidelines are capable of identifying neurotoxic substances, it would seem to be a small matter to consider chemicals tested by the Neurotoxicity Testing Guidelines or equivalent processes to be of low or little concern for neurotoxicity.

While these concerns may be considered a criticism of the Neurotoxicity Risk Assessment Guidelines, they existed prior to their development. With the publication of the Neurotoxicity Risk Assessment Guidelines, it is possible that some of these concerns will lessen because the guidelines provide a common set of principles for the EPA risk assessors to use. Up until now, risk assessors were without written guidance on the methods to be used for assessing chemicals for risk of neurotoxicity.

CONCLUSIONS

Risk assessment, as conceived by the NAS, involves a series of discrete steps that are intended to enhance the separation of the collection and interpretation of scientific information from the development of public policy decisions based on that information. The proposed Neurotoxicity Risk Assessment Guidelines fit into that process in that they are

intended to provide a conceptual framework for the interpretation of neurotoxicity data for the purpose of making risk assessment decisions.

The development and refinement of the proposed Neurotoxicity Risk Assessment Guidelines, like other risk assessment documents, is a continuing and evolving process. Previous drafts of these guidelines have undergone review by a number of groups both within and outside of EPA, and the guidelines have been revised accordingly in an attempt to address issues raised. When published in final form, the document is intended to provide for more consistent and transparent risk assessment decisions within and across the many offices of the EPA which must evaluate data on potential neurotoxicity. In addition to its intended use, the document may be used outside of the EPA by companies during product development and for product stewardship to anticipate how the EPA will interpret product safety data submitted to the Agency, and may serve as a basis for international efforts to harmonize risk assessment as well.

Concerns of EPA program offices are that the document helps in determining whether reported outcomes should be considered as adverse, and whether those outcomes can be attributed to neurotoxicity. Concerns of regulated industries include whether the document helps enough to clarify the interpretation of nonspecific outcomes, in particular of functional changes occurring at high-dose levels. In addition, another concern was that an overly conservative tendency in risk assessment prevents there from being a conclusion of sufficient evidence of no harm. These concerns should be considered in the revision and/or implementation of the Neurotoxicity Risk Assessment Guidelines.

All the participants in the workshop felt that, on the whole, the proposed Risk Assessment Guidelines would help provide more consistent, uniform, and appropriate decisions regarding potential neurotoxicity of compounds regulated by the EPA.

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