UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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September 9, 1988

OFFICE OF
THE ADMINISTRATOR

Honorable Lee M. Thomas
Administrator
U. S. Environmental Protection Agency
401 M Street, SW
Washington, D. C. 20460

Dear Mr. Thomas:

The Neurotoxicology Research Review Committee of the Science Advisory Board met February 29 and March 1, 1988 to review the program to develop neurotoxicity methods by the Neurotoxicology Division (NTD) of the Health Effects Research Laboratory (HERL) in Research Triangle Park, N.C.

The Committee concluded that NTD is the leading federal neurotoxicology research organization and, since its formation ten years ago, has assembled an excellent staff of capable research scientists who have established a significant record of contributions to the field. The Committee concludes that NTD can increase its effectiveness over the short and long term by implementing the following scientific and administrative recommendations:

Scientific Recommendations

1. Involve all NTD principal investigators in the development of more detailed long range planning for methods development research. This plan will narrow the scope of behavioral research currently underway in NTD and permit a more focused approach.

2. Establish a database for reference chemicals with known neurotoxic effects. Use these same reference chemicals as prototype chemicals for research in all areas.

3. Utlilize field batteries of behavioral and electrophysical tests in high-dose human exposure cases through interactions with other agencies with access to such cases (e.g. NIOSH and ATSDR).

4. Emphasize research on problems associated with screening tests for repeated low concentration exposure to potential toxicants.

5. Emphasize research on cross species extrapolation of toxicity data.

6. Confine the study of limbic system electrophysiological methods to secondary tests for risk characterization rather than using them as primary screening techniques.

Administrative Recommendations

1. Develop better mechanisms for assuring budget stability. Expenditures should be reviewed to assure that NTD is devoting its resources to its primary mission.

2. Encourage development of funding mechanisms to purchase equipment with unit costs between $15,000 and $50,000. At present the aquisition of such equipment is very difficult.

3. Reorganize the management structure responsible for the molecular toxicology elements of the program (including neurochemistry and neuropathology) to assure the optimal development and utilization of new techniques in this field. A separate branch might be formed for research in cellular and molecular toxicology.

The Committee was pleased to participate in this review and appreciates the opportunity to be briefed on the activites of the Neurotoxicology Division in the area of methods development. We request that the Agency consider the advice contained here and respond to our suggestions.

Sincerely,

Norton Nelson, Chairman
Executive Committee

Richard A. Griesemer, Chairman
Environmental Health Committee

Don McMillan, Chairman
Neurotoxicology Research
Review Committee

REVIEW OF NEUROTOXICOLOGY METHODS DEVELOPMENT BY NEUROTOXICOLOGY RESEARCH REVIEW COMMITTEE OF THE SCIENCE ADVISORY BOARD

The Neurotoxicology division (NTD) is the leading federal neurotoxicology research organization. Since its formation ten years ago, it has assembled an excellent staff of capable research scientists who have established a significant record of contributions to the field. The NTD should continue its leadership role in neurotoxicology and expand its overall impact on the field through the development of critical test methods and by addressing key issues that relate to the EPA mission. NTD has adapted, developed, and/or refined test methods that we would characterize as mainstream and, in some cases, innovative.

EXECUTIVE SUMMARY

As the leading federal neurotoxicology research organization, the NTD is a national asset. The NTD has focused its attention on the most appropriate potential effects of neurotoxic chemicals. It has developed and is validating a host of important methods for screening chemicals for neurotoxicity. These achievements are playing an important role in the regulatory process and in the protection of public health.

The next decade should be a major challenge for the NTD. The committee has made a number of recommendations which it feels will help NTD to meet this challenge. General recommendations include the development of better mechanisms for long range planning, increased cooperation among research groups (particularly with reference to coordinated attacks on prototypical chemicals), a stabilization of the patterns of funding which will allow controlled growth, the development of better mechanisms for the acquisition of equipment and supplies, and a better balance between long range programs and responses to emergency problems arising from EPA program offices.

The specific research groups have developed strong programs, although the groups could coordinate their research better than they have done. The Neurotoxicology Screening Program has developed and validated appropriate screening methods, particularly in behavioral toxicology. These method are now adequately developed to permit their use in testing chemicals of regulatory emphasis. Work with methods development and validation should continue with emphasis on cross species extrapolation.

The NTD has been particularly effective in developing electrophysiological methods. This effort should continue with emphasis on developing a data base for prototypical compounds, on the mechanisms underlying the evoked potential and on the interaction of prototypical chemicals with these mechanisms using

state-of-the-art technology. Certain of the methods under development, such as kindling procedures and evoked potentials in hippocampal slices should be confined to secondary tests for risk characterization, rather than being used as primary screens for risk identification.

The behavioral research program is among the most mature of NTD programs in terms of the development and validation of appropriate methods. The focus of this group should turn to the assessment of the consequences of repeated low-level exposure to chemicals and to the integration of their findings with those of other research groups.

The investigators working on methods for developmental neurotoxicity have developed sensitive and cost-effective methods. This group should focus on the study of prototypic chemicals using the methods that they have developed, giving the development of new methods a lower priority.

The program in molecular and cellular toxicology has made particularly impressive progress in developing a rat model of organophosphorous-induced delayed neuropathology and in activity correlating this neuropathology with neurotoxic esterase. They are also investigating the effects of neurotoxicants on neurotypic and proteins. This group should focus on intergrating its research program and findings with those of other groups.

The human functions research stands as a model program, since its data from animal tests seem to have direct application to similar human processes and the program has been designed with such efforts in mind. Efforts to field test the screening batteries in drug and chemical exposure groups should be a focus for the group.

The considerable research contributions of NTD are to be commended. Their work is generally of high scientific quality. The international recognition that NTD's research has obtained strongly reinforces EPA's decision to emphasize the development of this Division with the Health Effects Laboratory. If NTD gives careful attention to the long range planning of an integrated research attack on neurotoxicity problems and receives a stabilized budget which is adequate to permit reasonable growth during the next decade, the NTD should continue its leadership role.

GENERAL COMMENTS

1. A long range plan needs to be developed by NTD. The goals and objectives of the plan should be understood and supported by all managers and principal investigators. NTD has provided a collegial atmosphere in which multidisciplinary research can develop effectively, despite limitations in funds which may have hindered the development of some disciplines. While this atmosphere has avoided the limitations of most academic,

industrial, or government research institutes, the lack of long range planning appears to have led many NTD investigators to pursue their own research interests without requiring them to develop a common rationale for selecting and evaluating test methods. It appears that although the Division Director has a clear vision of the contributions of the NTD to the growth of the field of neurotoxicology and to the EPA mission, this vision is not always pursued by Branch management or the principal investigators who are essentially following their own research interests.

The lack of long range planning is a special concern since over half the staff has 8 years or less of experience beyond their Ph.D. While these more junior investigators are clearly able and well trained, their vision is necessarily limited by their experience. The committee recommends that NTD formulate a long term plan with well defined goals for the Division in methods development. It is important to recognize that long-term planning needs frequent review and reconsideration, but it is expected that the major goals of NTD would change infrequently. The limited experience of junior investigators in NTD suggests the need for an ongoing peer review process which may take the form of programmatic project review by a Division advisory group, or peer review of program initiatives by outside experts.

2. A fundamental impediment to the establishment of long range planning by NTD is the instability of its financial support. Unanticipated budget cuts with minimal prior notification have both discouraged NTD from attempts at long range planning and frustrated investigators. Greater budget stability would be an important factor in helping the Division to set and achieve long term goals. The level of funding for equipment and supplies significantly restricts the research and productivity of some scientists. The Committee recommends that NTD conduct a careful review of NTD expenditures, including on-site contract staff, cooperative agreements, and core research support. This would assure that an appropriate balance exists and that the limited funding available is directed toward those activities fundamental to NTD's mission. The Committee also recommends that consideration be given to finding funds for conferences such as those in 1969 and 1985 that addressed human test methods and test guidelines for screening. These served effectively to direct the field to respond to EPA's mission.

3. There is a need for certain equipment and supply items within the Division that is not being met. The difficulty in obtaining equipment items with unit costs in the range of $15,000 to $50,000 and the difficulty in running laboratories with extensive supply needs on a totally inadequate supply budget are two major problems that impede the ability of the Division to carry out its mission. It appears that the supplies budget is a major driving force and it appears that important research is not carried out because of its limits. The committee recommends that a funding mechanism be developed for equipment in the $15,000 to $50,000 range and that four layers of headquarters review not be imposed.

For example, reviews of on-line computer systems are carried out at headquarters by personnel who are totally ignorant of laboratory applications.

4. The organization of the branches is somewhat awkward, with molecular toxicologists reporting to behaviorists and physiologists. The disparity in disciplines may, at times, be detrimental to the development of the molecular toxicology programs, including description and explanation to upper management and competition for resources. The committee recommends that the Health Effects Research Laboratory management consider a minor administrative reorganization within the Division to assure the optimal development and utilization of new techniques in molecular toxicology (including neuropathology and neurochemistry).

5. Interactions between the Division and EPA program offices need to be improved. If the Division is required to respond to frequently changing priorities (e.g., the "crisis of the month") as defined by various program offices, a coherent program cannot be developed. The Division needs to be responsive to problems raised by program offices, but these short-term problems must be balanced against the Division's investment in achieving long term goals.

6. The Committee recommends that all research groups concentrate their research on the same prototype compounds. Much of the data on the effects of prototypical compounds on screening tests such as the functional observational battery may already be available in drug company files. The Screening for Neurotoxicity conference planned for April by the American College of Toxicology is a prototype of a mechanism for at least identifying such sources of data.

COMMENTS CONCERNING SPECIFIC METHODS

A. Neurotoxicology Screening Methods

The neurotoxicology screening program has been developing and validating a wide variety of screening tests for incorporation into a comprehensive test battery. Among the individual tests in the battery are the functional observation battery (FOB), automated testing of motor activity, and schedule-controlled behavior. The tests are validated by studying the effects of a series of known neurotoxicants in the battery in an attempt to develop profiles for different classes of neurotoxicants. This is a logical approach for detecting and classifying neurotoxicants.

The work published by the neurotoxicology screening group has been of high quality, with publications appearing in the better peer-reviewed journals. The group has a good command of the neurobehavioral toxicology literature and has developed a test battery that is consistent with the recommendations of various

select committees. Within the behavioral group, a critical mass of investigators has been recruited who have shown flexibility in their approach to problems in neurobehavioral toxicology.

The data developed by the screening group has had an important influence on the regulatory process in neurotoxicology. The methods developed by the group, and the chemical database it has generated, have influenced the recommendations made to the Agency for the development of neurotoxicity test guidelines. For example, members of the behavioral toxicology group presented their data to a recent meeting sponsored by the Office of Pesticides. The expert committee assembled by the Office of Pesticides made recommendations to that Office for neurotoxicity test guidelines under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) that depended heavily on the database developed in the Behavioral Toxicology Branch of NTD. Similarly, this database has influenced the test guidelines developed under the Toxic Substance and Control Act (TSCA).

Thus, the neurotoxicology screening group has been evaluating the appropriate tests and methods for behavioral toxicity testing and the data they have generated has influenced regulatory recommendations. Although this has been a useful approach, a coordinated research program on the neurobehavioral problems likely to arise during the next decade needs to be developed. For example, concerns that the Agency has about problems developing from long term low-level exposure to toxicants needs greater emphasis. There appears to be some lack of coordination across investigators in evaluating screening methods. For example, different chemicals are being evaluated for acute exposure, short-term repeated exposure and subchronic exposure thus making it difficult to determine the degree to which extrapolation can be made from acute to repeated exposure. Also, increased emphasis should be placed on species extrapolation to provide a basis for human risk assessment. In general, the research program is turning out high quality work, but the program needs better coordination and focus.

At least some of these difficulties may have been due to the level and variability of research funding. It is difficult to develop a focused plan of when budget cuts are being imposed with little advance warning.

In view of these strengths and weaknesses of the screening program the following recommendations are made:

1. The screening program should develop a planning process to determine which problems in neurotoxicology are likely to become important in the next decade, and how these problems can best be solved with the limited resources likely to be available.

2. Increased emphasis should be placed on problems and mechanisms associated with repeated, low level exposure to potential toxicants.

3. Where applicable, there should be greater research emphasis on cross-species extrapolation, particularly extrapolation to humans.

a. Since many of the difficulties in the development of extrapolation models may relate to cross-species differences in pharmacokinetics, the NTD should increases its efforts to develop pharmacokinetics research within the Division.

b. There is a need for closer cooperation and some integration of methods between those investigators developing animal models for neurotoxicity testing and those involved with human testing and epidemiology.

4. Efforts to validate the screening tests by studying the effects of a range of chemicals is encouraged. Efforts to characterize the toxicity through more detailed testing and to investigate the mechanisms underlying the toxicity are appropriate and should continue.

Given the poor predictive power of in vitro screening, and the limited available resources, the present efforts should be limited to two directions; 1) to become and stay knowledgeable about advances in this area and 2) to utilize appropriate methods for mechanistic studies of particular problems. It is not yet time to expend valuable resources in a broad effort on in vitro screening methods.

B. Electophysiological Approaches

The NTD is presently involved in research using electrophysiological methods with two major emphases: (1) sensory system toxicity and (2) limbic system activity. The research in sensory systems focuses on the visual and auditory systems. Three testing methodologies have been developed for testing the response of these systems to neurotoxic exposures. Flash-evoked potentials (FEP) and the pattern-reversal evoked potentials (PREP) assess the functional status of the visual system. The brainstem auditory evoked response (BAER) assess the functional status of the auditory system. Two approaches to limbic system function are also being evaluated. These include kindling, a model for a type of electrical activity in animals that closely resembles certain types of human epilepsy, and evoked potential analysis of the perforant path-dentate gyrus portion of the hippocampus.

1. Sensory Systems Research

An advantage of utilizing evoked potential analyses to monitor sensory system function is that a similar analyses can be conducted in many species, including man. In man, the techniques are noninvasive and involve recording of electrical activity from surface electrodes attached to the scalp. In animals, the electrode is usually implanted in the bone overlying the brain to provide a permanent, reusable recording site.

Present Status

Over the past 5-8 years, NTD has concentrated upon development of methods that would be suitable for hazard identification. Its efforts indicate that evoked potential approaches (FEP and PREP-visual system and BAER-auditory system) are useful for hazard identification. Evoked potentials reflect sensory system function and can detect perturbation in function associated with neurotoxic insults. The methods may detect neurotoxicity resulting from: 1) changes in receptor function, measured as changes in response threshold; 2) alteration of pathway integrity measured as alteration in parts of the evoked potential waveform or by changes in the latency of components of the response; 3) shifts in information processing function of the brain as measured by the amplitude of specified response components. NTD has provided evidence that evoked response techniques may also be sensitive to neural depression or excitation.

In addition to developing the specific methodology to test sensory function, NTD has also conducted research to validate test methodology and extend the methods to new problems. Important research has been initiated to improve the sensitivity and reliability of the test methods and to improve their efficiency and reduce costs. The lab has begun to establish a database, using reference chemicals, which is essential to defining testing reliability and redundancy. It has also provided a fairly complete analysis of the neurophysiological effects of selected substances such as the organotin compounds. Equally important, NTD is studying the basic physiology underlying the generation of the evoked response. It has completed important basic research into the generation of the components of the evoked response which enables the identification of specific regions of the brain involved in neurotoxic responses. One of the most significant areas of research has been the program to study effects of selected neurotoxicants in man and in animal models (rat). Such extrapolation studies are essential in validating the animal models, and in establishing their sensitivity relative to man.

Proposed Research

The investigators at NTD have outlined the following major areas for future research: 1) completion of a database employing reference compounds that encompass known neurotoxic mechanisms of action; 2) improving the understanding of the parallels between human and animal models to selected neurotoxic agents; 3) continuing basic research into the neural substrate underlying evoked responses; 4) refining test procedures to improve sensitivity and efficiency, reduce redundancy and reduce costs.

Recommendations

The committee recommends that NTD continue its program in this area with the following priorities:

1. A database should be establish using reference chemicals that encompasses the known neurotoxic effects. Reference chemicals should be selected to include known mechanisms of action. A data base is essential for hazard identification.

2. The physiological substrates responsible for generating the evoked potential should be established. An understanding of the mechanism underlying the measured response enables the identification of specific neuronal elements affected by the neurotoxicants.

3. Studies should be conducted to establish the parallels in responses of the human and animal model to selected neurotoxicants. This information will provide insight into the validity of the animal model and should indicate the relative sensitivity of the test species (rat) and the target species (man). This approach provides an important opportunity to obtain comparative data in man and animal.

4. The methodology for risk assessment should be continually refined. More research is needed to: a) determine what are the critical parameters to be measured; b) determine how redundancy can be reduced within and between procedures; c) improve sensitivity, stability and specificity of test methods to different types of neurotoxins; d) reduce time, labor and animals required to achieve a desired endpoint.

5. The group should be encouraged to provide data about the functional integrity of sensory systems for and use by the other groups in the division (behavior, neurochemistry, neuropathology, etc.). This will enhance interunit evaluation of various testing approaches.

6. The group and section head are encouraged to plan for the development of electrophysiologic approaches to more basic assessment of neurotoxic mechanisms. The appropriateness of state of the art technology (e.g. patch clamp, in vitro brain slice and cell culture systems) to the long term mission of the division should be addressed. The role that electrophysiology can play beyond methods development is one that must be addressed if the various components of the NTD are to grow and evolve in a smooth, consistent manner.

Limbic Systems Research

The limbic system is clearly sensitive to the effects many neurotoxic agents. Its suitability and usefulness in methods development as related to the mission of NTD has been evaluated to some degree both by in-house studies and cooperative agreements. There was concern as to the suitability of this

research for purposes of hazard identification. The two approaches to the limbic system function discussed here are kindling and hippocampal evoked potentials.

Kindling

Kindling (experimental siezures in animals) is time and labor intensive procedure. Its primary usefulness has been in providing an animal model of certain types of human epilepsy and it has been employed to a screen for anti-convulsant drugs. It has also been shown to be sensitive to certain convulsant drugs, including some pesticides. Although pesticides at low doses affect kindling, the Committee agrees with the consensus at NTD that this model is probably not suitable as a primary screening method in neurotoxicology; however, it may be useful as a secondary test for characterizing neurotoxicity, or it may be of value in assessing prenatal exposures on central nervous system development of the offspring, or assessing the consequences of repeated low level exposures to some chemicals. From the scientific literature available, kindling can be predicted to be most sensitive to neurotoxic actions that increase the excitability of the nervous system.

Hippocampal Evoked Potentials

The hippocampus is a suitable region of the nervous system for the study of evoked response analysis, particularly of the monosynaptic perforant path dentate gyrus response. Evoked responses of the region can be evaluated both in vitro (hippocampal slices) and in vivo. The approaches have different but complementary uses. Research done by the group has suggested that the hippocampal slice is not a suitable method for primary screening for neurotoxicity. The Committee agrees with this opinion. The Committee feels that these methods are more profitably employed in studies defining mechanisms of toxic action than in screening. A data base for hippocampal evoked responses would be useful for comparison with data from other testing procedures. Filling this data gap might help to delineate the future role of these approaches for the NTD.

Recommendation

For hippocampal-ER-kindling methods, the Committee recommends that these procedures not be used as primary screening tests for hazard identification. They may be of value, however, for characterization of developmental effects and/or repeated, low level exposure effects of neurotoxins. Alternative approaches should be considered carefully because these approaches are time and labor-intensive. The in vitro hippocampus preparation should be validated with prototype compounds before it is used widely.

C. Behavioral Research

It has now been recognized that neurotoxicology screening, with available methods, can be done by studying the behavior of

target organisms and interactions with their environment. Deficits in memory, coordination, judgment, or in response to environmental changes represent threats to ability to function efficiently or even to survive. One phase of the NTD program is directed, for these reasons, at assessments of such behavior.

Originally, NTD was charged with developing suitable assessment methods for behavioral toxicology. A legacy of that original mission is an impressive range of procedures, several of which have demonstrated their utility as neurotoxic endpoints.

This original investment in test method validation and refinement has now advanced to a stage at which it can serve an a source for undertaking a major responsibility of NTD -- risk characterization. Further methodological developments should not be precluded, of course, but the focus should begin to change from methods development to the use of the methods already developed is risk characterization. Such a shift in priorities would enable NTD to move into a pivotal position in the new RURA initiative.

At present, those aspects of the program devoted to what is broadly called, "cognitive behavioral research" encompass a variety of procedures, each aimed at some aspect of behavior such as attention, learning, memory, discrimination, and so on. Within each of these categories, several experimental approaches are discussed. As a result, techniques tend to proliferate, but at some cost to depth of analysis and understanding. A limited range of chemicals is surveyed, and important parametric manipulations are not explored.

One consequence of the tendency to proliferate tests has been the emphasis on short-term, high-dose treatment. EPA is continually embroiled in disputes about the validity of extreme doses in projecting cancer risks on the basis of animal studies. Parallel disputes are certain to arise when the program for reducing uncertainty in risk assessments (RURA) begins to deal with neurotoxicity, unless the appropriate data are available. NTD is uniquely equipped to respond to these future needs of the agency, but it has to pursue an explicit policy of appropriate research to do so. Bending the current work on thermoregulation, maze performance, flavor avoidance, and delayed response to these aims will enhance both the research and its utility to the agency.

The Committee recommends that the scope of research activities be narrowed to permit a more focused approach. Such a narrowing would permit NTD scientists to respond to questions of concern to the agency; e,g, (1) Can behavioral endpoints be used to trace the progressive consequences of research exposure? (2) As toxicity unfolds, what is the correspondence between behavioral, neurochemical, and morphological measures? (3) Would more detailed analyses of behavioral measures afford an improved basis for the kinds of extrapolation required for risk assessment?

In summary, the committee views the future of behavioral research at NTD as closely related to the risk evaluation process. In accord with this view, it recommends that the Principal Investigators responsible for these programs adopt a focused research plan, and carefully consider integration with other disciplines within NTD.

D. Developmental Methods

The investigators working on methods to identify and describe developmental neurotoxicity are a talented, well-trained group who have done a good job of identifying and implementing promising test methods. They have developed test methods that are cost-effective and sensitive. Scientifically, they are productive and in touch with their fields. They interact well with each other and with colleagues outside the agency.

The group has been less successful at developing a strategy for assessing the usefulness of the methods that they have selected. We recommend that they do the following:

1. The group, in conjunction with other groups, should construct a standard list of toxic and non-toxic agents to use in methods evaluation. The list should include prototypical agents whose effects have been well-characterized. They should represent agents producing a variety of injuries and mechanisms of injury. Active agents should be tested before proceeding to screen inactive agents or unknowns.

2. Exposure regimens (or set of regimens) appropriate to damage the developing nervous system should be used.

3. The group should perform a logic analysis which specifies the possible outcomes of the proposed experiments and the conclusions about methods which will be drawn from those outcomes.

4. The evaluation of methods should be given a high priority with the development of new methods receiving a lower priority. Because new methods appear constantly, the failure to do this will result in an endless enlargement of the methods catalogue. The goal should be a reduction of this catalogue to those methods most valuable for toxicity testing.

E. Molecular and Cellular Toxicology

The development of a program in immunocytochemistry is commendable. Where possible, it is recommended that close coordination between these studies and those involving biochemical markers be established as a means of validating the biochemical markers more efficiently.

The development of molecular and cellular indices of toxic neuropathies is considered particularly promising. However, the complexity of such systems will require critical outside

collaborative support, and it is recommended that this be given priority.

The axonal transport project has the potential for providing a sensitive index of toxicity, as well as being of mechanistic importance. It is recommended that emphasis be placed upon validation of these methodologies.

1. Neuropathology

A particularly important direction of this group has been studies into the biochemistry of NTE. Such studies involve protein purification and characterization, and their technical difficulties are exacerbated by the nature of the NTE differential assay. While such experiments are not guaranteed to be successful, the remarkable correlation of NTE activity (a differential enzymatic measurement) with organophosphorous-induced delayed neuropathy (OPDIN) makes these experiments long overdue. This direction should be encouraged and may be one excellent project in which outside assistance (either through cooperative agreement, consultants, or RFP) would be appropriate.

Previously, it was believed that OPIDN, an important neurotoxic effect in humans, could not be produced in the rat. Thus, the chicken has been the accepted model, both increasing the cost of studies and preventing use of the large body of neurobiological and toxicological data in the rat. However, the group at NTD had developed data suggesting that an OPIDN-like neuropathology can be obtained in the rat. However, the rat clearly differs from the human and chicken; much higher doses of organophosphate compounds are needed, and the pathology is not accompanied by the same degree of incapacitation. Nonetheless, there are potential applications for such a model, and further validation and study should be a high priority.

As these examples indicate, the research directions in neuropathology are strong and clearly related to the mission of NTD and the Agency. There was, however, a lack of integration of this group with other disciplines. This probably is a result of the lack of long term planning through the NTD, as well as competition for resources.

Neurochemistry

The neurochemistry group brings several important strengths to the activities of the NTD. The investigators are individually strong, and have picked topical areas for their research. For example, the effects of various neurotoxicants on neurotypic and gliotypic proteins is an important subject to understand, and the investigators should be commended for this approach. However, they have emphasized this approach as a general marker of neurotoxicity, rather than as important biochemical loci whose function needs to be understood (and which later might produce such a marker). Nonetheless, these competent investigators are likely to produce important information which will be even more

useful if integrated into behavioral, physiological, and pathological studies ongoing elsewhere in the NTD.

As with the neuropathology group, this group should integrate their research with that of the other research groups. There were cases where the significant expertise of this group could have been integrated into projects ongoing by other sections (such as with the pyrethroids).

F. Human Function Research

Methods development efforts in the area of human function have concentrated on specific Agency needs for screening tests and test batteries which can be used to assess exposures from waste dumps or chemical spills posing a hazard to the nervous system. Portable batteries of behavioral and electrophysiological tests have been developed through NTD support and the program staff recognizes the need to apply these batteries in field situations to known neurotoxicants following accidental exposures to assess battery usefulness under actual field conditions.

The sensory testing program displays good breadth and depth. The addition of speech perception to classic audiometry recognizes the need to assess the processing capability for patterned sounds by adopting the most important real-life application of sound patterns. The development of olfactory trigeminal test capabilities is also important, because of the unique status of this system as a warning indicator of environmental exposures. The implementation of a tactile sensitivity test device provides a screening test for peripheral neuropathy, one of the problems identified most frequently following significant chemical exposures. Because of the doubts about the validity of the proposed device, however, it should not be adopted without a thorough validation study. The visual and auditory testing programs, however, are among the most forward-looking in the Division because they assess key visual functions and effectively integrate test methods for humans and animals. This should be seen as a model for NTD research because it offers an animal model which can be used in high-dose laboratory research to identify neurotoxic chemicals in pre-market screening with confidence that the application to humans is direct. In addition, the low end of the dose-effect curve can be assessed in human laboratory research, or, if an accidental spill/exposure occurs, in affected individuals. This model should be extended to other programs and test paradigms in NTD.

The future direction of methods development in this program is sound, aiming at field evaluation and validation of the screening batteries and laboratory validation of selected sensory tests. Specific Committee recommendations are: 1) field testing should be pursued in high-dose exposure cases in industrial or agricultural settings; 2) test batteries should be validated using acute drug exposures and clinical populations; 3) plans should be made to add vestibular test methods to provide

capabilities for a more complete sensory analysis. (This is a good direction as the hardware and software are available and there is data on a range of environmental chemicals that demonstrate unique effects using these test systems); 4) the group should adopt the Neurobehavioral Evaluation System (NES) for testing children as planned. However, careful attention should be given to a rationale for selecting tests to adopt from the many available in the NES. Possible rationales would be to select tests sensitive to generally accepted behavioral taxonomies derived from factor analytic studies (Fleischman/Carroll) or tests sensitive to frequently-occurring neurotoxic effects; (5) opportunities should be sought to integrate human and animal test methods in ways similar to visual function testing that would require long-term planning of cooperative research goals among the various research specialists in NTD.

Science Advisory Board
Neurotoxicology Research Review Committee

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