

may affect different cases, consistent but not necessarily identical risk management decisions must be made on a case-by-case basis. These Guidelines are not intended to give guidance on the nonscientific aspects of risk management decisions.

F. Summary and Research Needs

These Guidelines summarize the procedures that the U.S. Environmental Protection Agency would use in evaluating the potential for agents to cause neurotoxicity. These Guidelines discuss the general default assumptions that should be made in risk assessment for neurotoxicity because of gaps in our knowledge about underlying biological processes and how these compare across species. Research to improve the risk assessment process is needed in a number of areas. For example, research is needed to delineate the mechanisms of neurotoxicity and pathogenesis, provide comparative pharmacokinetic data, examine the validity of short-term in vivo and in vitro tests, elucidate the functional modalities that may be altered, develop improved animal models to examine the neurotoxic effects of exposure during the pre-mating and early post-mating periods and in neonates, further evaluate the relationship between maternal and developmental toxicity, provide insight into the concept of threshold, develop approaches for improved mathematical modeling of neurotoxic effects, improve animal models for examining the effects of agents given by various routes of exposure, and address the synergistic or antagonistic effects of mixtures of chemicals and neurotoxic response. Such research will aid in the evaluation and interpretation of data on neurotoxicity and should provide methods to assess risk more precisely.

VII. References

- Adams, J.; Buelke-Sam, J. (1981) Behavioral testing of the postnatal animal: testing and methods development. In: Kimmel, C.A.; Buelke-Sam, J., eds. *Developmental toxicology*. New York: Raven Press, pp. 233-238.
- Anger, W.K. (1984) Neurobehavioral testing of chemicals: impact on recommended standards. *Neurobehav. Toxicol. Teratol.* 6:147-153.
- Anger, W.K. (1986) Workplace exposures. In: Annau, Z.A. ed., *Neurobehavioral toxicology*. Baltimore: Johns Hopkins University Press, pp. 331-347.
- Anger, W.K. (1990) Worksites behavioral research: results, sensitive methods, test batteries, and the transition from laboratory data to human health. *Neurotoxicology* 11:627-718.
- Anger, K.; Johnson, B.L. (1985) Chemicals affecting behavior. In: O'Donoghue, J., ed. *Neurotoxicity of industrial and commercial chemicals*. Boca Raton, FL: CRC Press.
- Barnes, D.G.; Dourson, M. (1988) Reference dose (RfD): description and use in health risk assessments. *Regul. Toxicol. Pharmacol.* 8:471-486.
- Bondy, S.C. (1986) The biochemical evaluation of neurotoxic damage. *Fundam. Appl. Toxicol.* 6:208-216.
- Boyes, W.K. (1992) Testing visual system toxicity using visual evoked potential technology. In: Isaacson, R.L.; Jensen, K.F., eds. *The vulnerable brain and environmental risks, Vol. 1: Malnutrition and hazard assessment*. New York: Plenum, pp. 193-222.
- Boyes, W.K. (1993) Sensory-evoked potentials: measures of neurotoxicity. In: Erinoff, L., ed. *Assessing the toxicity of drugs of abuse*. NIDA Research Monograph 136. National Institute on Drug Abuse, Alcohol, Drug Abuse and Mental Health Administration, U.S. Department of Health and Human Services, pp. 63-100.
- Buelke-Sam, J., Kimmel, C.A.; Adams, J. (1985) Design considerations in screening for behavioral teratogens: results of the collaborative teratology study. *Neurobehav. Toxicol. Teratol.* 7:537-589.
- Callender, T.J.; Morrow, L.; Subramanian, K. (1994) Evaluation of chronic neurological sequelae after acute pesticide exposure using SPECT brain scans. *J. Toxicol. Environ. Health.* 41:275-284.
- Carson, B.L.; Stockton, R.A.; Wilkinson, R.R. (1987) Organomercury, lead, tin compounds in the environment and the potential for human exposure. In: Tilson, H.A.; Sparber, S.B., eds. *Neurotoxicants and neurobiological function: effects of organoheavy metals*. New York: J. Wiley, pp. 1-80.
- Coles, C.D.; Brown, R.T.; Smith, I.E.; Platzman, K.A.; Erickson, S.; Falek, A. (1991) Effects of prenatal alcohol exposure at school age I. Physical and cognitive development. *Neurotoxicol. Teratol.* 13:357-367.
- Cory-Slechta, D.A. (1989) Behavioral measures of neurotoxicity. *Neurotoxicology* 10:271-296.
- Costa, L.G. (1988) Interactions of neurotoxicants with neurotransmitter systems. *Toxicology* 49:359-366.
- Crump, K.S. (1984) A new method for determining allowable daily intakes. *Fundam. Appl. Toxicol.* 4:854-871.
- Davis, J.M.; Svendsgaard, D.J. (1990) U-shaped dose-response curves: their occurrence and implication for risk assessment. *J. Toxicol. Environ. Health* 30:71-83.
- Dyer, R.S. (1985) The use of sensory evoked potentials in toxicology. *Fundam. Appl. Toxicol.* 5:24-40.
- Dyer, R.S. (1987) Macrophysiological assessment of organometal neurotoxicity. In: Tilson, H.A.; Sparber, S.B., eds. *Neurotoxicants and neurobiological function effects of organoheavy metals*. New York: J. Wiley, pp. 137-184.
- Eccles, C.U. (1988) EEG correlates of neurotoxicity. *Neurotoxicol. Teratol.* 10:423-428.
- Ecobichon, D.J.; Joy, R.M. (1982) Pesticides and neurological diseases. Boca Raton, FL: CRC Press, pp. 151-203.
- Ecobichon, D.J.; Davies, J.E.; Doull, J.; Ehrich, M.; Joy, R.; McMillan, D.; MacPhail, R.; Reiter, L.W.; Slikker, W., Jr.; Tilson, H. (1990) Neurotoxic effects of pesticides. In: Baker, S.R.; Wilkinson, C.F., eds. *The effect of pesticides on human health*. Princeton, NJ: Princeton Scientific Publishing Co., Inc., pp. 131-199.
- Friedlander, B.R.; Hearn, H.T. (1980) Epidemiologic considerations in studying neurotoxic disease. In: Spencer, P.S.; Schaumberg, H.H., eds. *Experimental and clinical neurotoxicology*. Baltimore: Williams and Wilkins, pp. 650-662.
- Gad, S.C. (1982) A neuromuscular screen for use in industrial toxicology. *J. Toxicol. Environ. Health* 9:691-704.
- Gad, S.; Weil, C.S. (1988) Statistics and experimental design for toxicologists, 2nd ed. Caldwell, NJ: Telford Press.
- Gaylor, D.W.; Slikker, W. (1990) Risk assessment for neurotoxic effects. *Neurotoxicology* 11:211-218.
- Glowa, J.R. (1991) Dose-effect approaches to risk assessment. *Neurosci. Biobehav. Rev.* 15:153-158.
- Goldberg, A.M.; Frazier, J.M. (1989) Alternatives to animals in toxicity testing. *Sci. Am.* 261:24-30.
- Goldstein, M.K.; Stein, G.H. (1985) Ambulatory activity in chronic disease. In: Tryon, W.H., ed. *Behavioral assessment in behavioral medicine*. New York: Springer Publishing Co., pp. 160-162.
- Griffin, J.W. (1990) Basic pathologic processes in the nervous system. *Toxicol. Pathol.* 18:83-88.
- Hayes, W.J. (1982) Pesticides studied in man. Baltimore: Williams and Wilkins.
- Hughes, J.A.; Sparber, S.B. (1978) *d*-Amphetamine unmasks postnatal consequences of exposure to methylmercury in utero: methods for studying behavioral teratogenesis. *Pharmacol. Biochem. Behav.* 8:365-375.
- Jacobson, S.W.; Fein, G.G.; Jacobson, J.L.; Schwartz, P.M.; Dowler, J.K. (1985) The effect of intrauterine PCB exposure on visual recognition memory. *Child Dev.* 56:853-860.
- Jarabek, A.M.; Menache, M.G.; Overton, J.H.; Dourson, M.L.; Miller, F.J. (1990) The U.S. Environmental Protection Agency's inhalation RfD methodology: risk assessment for air toxics. *Toxicol. Ind. Health* 6:279-301.
- Johnson, M.K. (1990) Organophosphates and delayed neuropathy—Is NTE alive and well? *Toxicol. Appl. Pharmacol.* 102:385-399.