Acta Physiologica Hungarica, Volume 87 (1), pp. 67–70 (2000)

Risk assessment of neurotoxic pesticides

Kornélia **Lehotzky**

"Fodor József" Public Health Center, National Institute for Chemical Safety, Budapest

Received: July 7, 1999
Accepted: February 23, 2000

In order to establish safe exposure levels for toxic chemicals, risk assessment guidelines have been developed.

A compilation is given by the author on the elements of risk assessment of hazardous neurotoxic pesticides, using data obtained from human epidemiological studies, from animal experiments, from the international literature and from the author's own experiments as well. Well-controlled laboratory studies of neurotoxicity have the potential to provide adequate exposure and effect data for accurate hazard identification. Animal models of neurotoxicity as highly sensitive behavioral and neurophysiological methods as a function of doses, provide data for human low dose extrapolation by using mathematical models. This procedure might be the basis for reducing risk ("risk management"), therefore some examples are given, how to handle properly neurotoxic pesticides with different- high or low-risk.

Keywords: risk assessment, neurotoxicity, pesticides

Agencies and programmes have been established to deal with risk assessment of hazardous chemicals, including pesticides.

In order to evaluate the human health consequencies, the field of risk assessment has been developed during the past decade. Their focus were not only acute, but long-term effects, including noncancer endpoints such as neurotoxicity [1].

Recent evidence indicates that exposure to neurotoxic agents, as neuroleptics, tranquillants, heavy metals and drugs of abuse might cause serious health problems. The manifestation of neurotoxicity, the chemical induced changes in the structure and function of the nervous system can be observed as alterations in sensory, motor or cognitive functions. These methods could be used to set exposure guidelines for other neurotoxic chemicals, and behavioral toxicology can provide sensitive, reliable data for risk assessment.

Correspondence should be addressed to
Kornélia Lehotzky
H-1113 Budapest, Ulászló u. 39/41, Hungary

Presented at the LXIVth Annual Meeting of the Hungarian Physiological Society, Budapest, July 5–8, 1999

Process and methods

Principles of risk assessment for neurotoxicity are evolving rapidly. At the present time, neurotoxicity risk assessment is generally limited to quantitative hazard identification, and the relative probability can be calculated. The risk assessment process involves four steps, namely hazard identification, dose-response assessment, exposure assessment and risk characterization [2, 3].

Hazard identification: those agents that adversely affect stuctural and/or functional integrity of the nervous system expressed in modified behavior may be classified as neurotoxicants. Information should be obtained from human studies, like accidents or case reports and epidemiological studies – using biomarkers for estimating exposure and effect – as well as animal studies.

Animal studies: as part of safety evaluation [4], animal models are widely used and the results are extrapolated to humans. The application of tiered testing advisable, is as follows:

behavioral endpoint: gait, sensorimotor reflex, motor activity, behavior, changes in motor coordination, swimming ability in stress situation, different signs as weakness, paralysis, tremor ect., changes in touch, sight, sound, taste and smell sensations.

Changes in learning ability and memory functions tested in different tasks are as follows: conditioned reflex acquisition and extinction (habituation), for testing of reversibility or long-lasting deficits-repeated acquisition or reacquisition. Moreover behavioral patterns in open field and maze are included in different test batteries, too. Cognitive and associative processes should be demonstrated during learning and habituation of different conditioned reflex trials, by altered performance and/or lengthened reaction time (latency period).

The experimental animal, usually the rat, inspite of being less sensitive to neurotoxicants, than the primates, often serves as its own control. Usually matched pair control group should be used parallelly. Some examples for highly sensitive methods, widely used by neurotoxicological laboratories, as well as by the author itself [8] are as follows:

– swimming test in stress-situation (preceded by amphetamin treatment for increasing motor activity) according to Porsolt's method.

– conditioned avoidance – escape – learning, reflex acquisition and extinction, according to Cook and Weidley's method.

– social behavior in figure-eight maze, tested in animal pairs according to Dyer's method [5].

Neurophysiological endpoint: maximal motor or sensory nerve conduction velocity, as an index of axon degeneration or demyelination process, which could be measured by detecting response amplitude and latency period comparing to control values, in rat tail nerve, using Miyoshi's method.

Minimal brain dysfunction: exposure to chemicals during development, can result in neurotoxicity in offspring' (including lead, mercury, amphetamine, ethanol, drugs of abuse, organophosphate insecticide e.g. fenithrotion, organospolvents e.g. carbon-disulfide etc.). The so-called minimal brain dysfunction (MBD), or behavioral teratogenicity manifested postnatally as subtle, long-lasting or reversible behavioral dysfunction [6], as a sign of delayed development.

Animal to human extrapolation serves as basis to predict hazards by using uncertainty factors, to adjust sensitive species, sex, age and populations, or lack of data. Dose-response assessment might involve determination of no adverse effect level (NOAEL) or benchmark dose (BMD), where threshold might be defined, when the mechanism of action is the same for all doses and species [7].

Low dose extrapolation by mathematical models should be used to predict "de minimis risk", to obtain precise value for acceptable risk, where no manifested health disorders – adversed effects – could be observed.

Risk management, risk reduction should be performed after taking all these factors into consideration, by calculation of relative risk for the most sensitive human population, taking the "worst case" into account.

Results and conclusion

Some examples for neurotoxic pesticides, where risk assessment should performed to reduce risk are as follows:

Organomercurials, including fungicides: are persistent in soil, water, see-food and food-chain, they cause severe human intoxication in Japan among fishermen of Minamata bay, being manifested as irreversible sensory, motor (as "segmental demyelination") and visual disorders. They are SH-active and highly neurotoxic in every species, moreover might cause minimal brain dysfunction (behavioral teratogenic).

Risk of neurotoxic action is extremely high, therefore they are available for experts only. In Hungary using of organomercurial seed dressing fungicides were banned in 1974, based on our laboratory results, where memory and learning disorders were found in rats, moreover severe slowing down of maximum motor conduction velocity of the sciatic nerve of rabbits has been demonstrated after subacute, low dose administration of the fungicide metoxi-ethyl-mercury-chloride [11].

Organophosphate cholinesterase inhibitor pesticides cause severe cholinergic signs, after acute intoxication – cholinesterase inhibition in red blood cells and/or in serum.

Some of them (e.g. fenitrothion) might cause delayed neurotoxicity. That manifested in slowing down of maximum motor conduction velocity on rats and rabbits as well, as it has been shown in our laboratory, as a function of "dying-back" demyelination of sensory-motor nerves, as irreversible damage [12]. Atropin has no antidotal effect against this process. Risk of neurotoxicity is high, therefore they are available for experts only.

Pyrethroids: Synthetic pyrethroids widely used and popular house-hold insecticides, having relatively low mammalian acute toxicity, cause increased firing of nerve cells. However, pyrethroids, containing cyano-groups, might cause severe but reversible paresthesia and anesthesia when dermal exposure occurres.

Therefore advisable to handle with care, only for educated people, because of their – however low – risk of neurotoxicity.

Acknowledgements

Author is grateful for helping and advices to Mr. Hugh Tilson (EPA) and Mr. Zoltan Annau (Johns Hopkins University).

REFERENCES

1. USEPA: Final report: Principles of Neurotoxicity Risk Assessment in: Federal Register **59**, No 158 (1994).
2. Elements of Toxicology and Chemical Risk Assessment Environ Corp. New Jersey, USA 1986.
3. Faustman, E. M., Omenn, G. S.: Risk Assessment in: Casarett and Doulls "Toxicology". Fifth Ed. Ch. 4. pp 75–88 (1996).
4. OECD: Guidelines for Testing of Chemicals, Paris, 1994.
5. Tilson, H. A.: Screening for Neurotoxicity, Principles and Practice J. Am. Coll. Toxicology **8**, 13–17 (1983).
6. Woodward, K. N.: Hazard Identification, Risk Assessment, Regulation and Legislation. in: Toxicology and Principles CRC Press, Washington, 1996.
7. Lehotzky, Kornélia: Animal models for Testing of Behavioral Teratogenicity of Neurotoxic Chemicals. Doctor Thesis, Hungarian Academy of Sciences, 1990, Budapest.
8. Lehotzky, Kornélia: Animal Models for Assessment of Neurotoxicity Central European J. of Occupational and Environmental Medicine **3**(4), 323–326 (1997).
9. Lehotzky, Kornélia: Applied Toxicology: Factors Affecting of Human Risk Assessment of Chemicals, Risk Reduction, (in Hungarian). Egészségtudomány **XLIII**, 97–102 (199).
10. Annau, Zoltán: Behavioral Toxicology and Risk assessment. Neurotoxicol. and Teratol. **12**, 547–551 (1990).
11. Lehotzky, Kornélia: Neuro- and Nephrotoxicity of Fungicide Methoxi-ethyl-mercury-chloride, Ph.D. Thesis, Budapest, 1972.
12. Lehotzky, Kornélia, Szeberényi, M., Kiss, J. A.: Behavioral Consequencies of Prenatal Exposure to the Organophosphate insecticide Sumithion. Neurotoxicol. and Teratol. **11**, 321–324 (1989).