Animal Models of Environmentally Induced Memory Impairment[a]

H. L. EVANS, P. J. BUSHNELL, M. J. PONTECORVO,[b] AND J. D. TAYLOR

Institute of Environmental Medicine
New York University Medical Center
New York, New York 10016

Cognitive dysfunction has been reported as a consequence of occupational exposure to chemicals such as metals and solvents.[1,2] It is difficult to identify the causative agent in these clinical cases because of ethical restrictions on performing experiments with humans and because of numerous confounding variables in occupationally exposed populations (e.g., alcohol and drug use, health status, and exposure to a wide variety of industrial chemicals).

In spite of the obvious impact of industrial products upon the nervous system, toxicologists have only begun to measure and interpret cognitive function in animals. Pharmacologists, on the other hand, have relied heavily upon single-response, one-trial tests (e.g. passive avoidance), which are not effective in separating the non-specific effects of drugs and toxicants measured as rate and speed from specific effects upon cognition. More suitable are operant, multiple-choice measures of accuracy, a less ambiguous index of cognitive function than speed. These issues were reviewed more fully by Evans and Daniel.[3] We therefore developed experimental models of cognitive dysfunction with the macaque monkey, which closely resembles the human in both cognitive function and in response to drugs and toxicants.[4,5] Also, pigeons were used as an alternative model because they are economical and yet capable of complex cognitive behavior.[6,10]

A three-choice, variable-delay matching-to-sample (DMS) procedure provided an objective and challenging test of short-term memory. Both monkeys and pigeons were trained to perform the DMS for positive reinforcement before exposure to toxicants and drugs began. The retention interval (delay between the presentation of the sample stimulus and the choice stimuli) was manipulated to provide psychophysical evidence of specificity of any changes in matching performance. Animals were tested in a three-choice appetitive procedure, an improvement over two-choice procedures in that a wider range of baselines can be obtained and evidence of non-specific effects such as position bias is more easily documented. Performance tests of this type circumvent the cultural bias of many human tests and may thus provide an important thread of continuity between the clinic and the laboratory. We now summarize preliminary results to be published in detail elsewhere.

Delayed matching of previously trained pigeons was evaluated following daily inhalation of toluene or *n*-hexane. Inhalation of 3,000 ppm toluene reduced matching

[a]Animal care conformed to the National Institutes of Health Guide. Supported by National Institutes of Health Grant OH-00973, ES-03461, Training Grant ES-07065, and Center Grant ES-00260.

[b]Present address: Department of CNS Research, Bldg. 56, Lederle Labs., Pearl River, NY 10965.

accuracy after one to two weeks of daily exposure; recovery occurred within two weeks after the exposure stopped. The effect of toluene was greater at longer retention intervals. Inhalation of *n*-hexane at concentrations up to 3,000 ppm did not affect DMS of pigeons or monkeys. Monkeys showed no observable effects of toluene up to 1,000 ppm.

Acute inhalation of toluene by monkeys during performance of the DMS task produced a different type of impairment. Unlike the gradually emerging deficit observed in animals tested following each repeated exposure, testing during acute exposure to toluene produced immediate decrements in both accuracy and reaction time. These deficits were constant across retention intervals, suggesting disruption of attention and/or motivation, rather than short-term memory.[7]

Alkyltins represent another occupational health hazard that may involve impaired cognition. A decrement in DMS occurred in monkeys and pigeons 5–7 days after acute oral exposure to trimethyltin. Monkeys were affected by 0.5 mg/kg trimethyltin, while the minimum effective dose for pigeons was 2.0 mg/kg. Impaired DMS in monkeys occurred in the absence of other toxic signs, suggesting that the monkey may provide a more specific model of trimethyltin-induced memory impairment than does the pigeon.[8]

These early findings, and work currently in progress, confirm our ability to measure cognitive behavior in experimental animal models. Such models provide a means to assess the impact of occupational health hazards on cognition, as well as an experimental paradigm for evaluating potential therapeutic compounds.[9,10]

REFERENCES

1. ELOFSSON, S.-A., F. GAMBERALE, T. HINDMARSH, A. IREGREN, A. ISAKSSON, I. JOHNSSON, B. KNAVE, E. LYDAHL, P. MINDUS, H. E. PERSSON, B. PHILIPSON, M. STEBY, G. STRUWE, E. SODERMAN, A. WENNBERG & L. WIDEN. 1980. Exposure to organic solvents. A cross-sectional epidemiological investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. Scan. J. Work Environ. Health **6:** 239–273.
2. FORTEMPS, E., G. AMAND, A. BOMBOIR, R. LAUWERYS & E. C. LATERRE. 1978. Trimethyltin poisoning: A report of two cases. Int. Arch. Occup. Environ. Health **41:** 1–6.
3. EVANS, H. L. & S. A. DANIEL. 1984. Discriminative behavior as an index of toxicity. Adv. Behav. Pharmacol. **4:** 257–283.
4. EVANS, H. L. & B. WEISS. 1978. Behavioral toxicology. *In* Contemporary Research in Behavioral Pharmacology. D. E. Blackman & D. J. Sanger, Eds.: 449–487. Plenum Publishing Corp. New York.
5. EVANS, H. L. 1982. Assessment of vision in behavioral toxicology. *In* Nervous System Toxicology. C. L. Mitchell, Ed.: 81–107. Raven Press. New York.
6. TEAL, J. J. & H. L. EVANS. 1982. Effects of DDAVP, a vasopressin analog on delayed matching behavior in the pigeon. Pharmacol. Biochem. Behav. **17:** 1123–1127.
7. TAYLOR, J. D. 1984. Thesis for M.S. degree. N.Y.U. Medical Center.
8. BUSHNELL, P. J. & H. L. EVANS. 1984. Trimethyltin-induced memory impairment in nonhuman primates. Fed. Proc. **43:** 763.
9. PONTECORVO, M. J. & H. L. EVANS. 1985. Effects of antiracetam upon the delayed matching-to-sample performance of monkeys and pigeons. Ann. N.Y. Acad. Sci. (This volume.)
10. PONTECORVO, M. J. & H. L. EVANS. 1985. Effects of aniracetam on delayed matching-to-sample performance of monkeys and pigeons. Pharmacol. Biochem. Behav. **22.**