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

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5/18/84

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Human Cholinesterase Study
Tox. Chem. 219AA
TO: Jay Ellenberger, PM#12
Registration Division (TS-769)

FROM: Gary J. Burin, Toxicologist GB 5/18/84
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Recommendation: It is recommended that this study be classified as Supplemenry Data. Although the number of subjects in this study is small (4) and only males were tested, a LEL for plasma ChE of 0.10 mg/kg/day is indicated which is accompanied by clinical signs of ChE inhibition. The apparent NOEL is 0.03 mg/kg/day. RBC ChE inhibition is not observed at any dose level. It is also recommended that this study, despite its limitations, play important role in the establishment of the ADI for chlorpyrifos.

Review of Data:

Three-Week Toxicity Study with Cholinesterase Determinations, Humans. Conducted by Albany Medical College, Albany, New York, March 1972 and submitted by Dow Chemical, April 6, 1984.

Sixteen human volunteers were selected from the Clinton Correctional Facility in Dannemora, N.Y. and were subjected to a thorough physical examination which included ECG, urinalysis, chest x-ray, urinalysis, hematology and clinical chemistry.

The volunteers were (apparently randomly) divided into 4 experimental groups which received daily doses of either 0, 0.10, 0.030, or 0.014 mg/kg of body weight of Dowco 179 (purity not specified) via oral ingestion of the test material "in tablet form". Four individuals were assigned to each group. The tablets were administered once each day at the time of breakfast. Blood samples were taken twice each day from each volunteer for cholinesterase measurements and weekly for hematology and clinical chemistry measurements. Urinalysis was also conducted on a weekly basis. Treatment continued daily for a 7 week period for the control group, 9 days for the 0.10 mg/kg/day group, , 20 days for the 0.03 mg/kg/day and 27 days for the 0.014 mg/kg/day dose group.

Results:

Clinical signs of cholinesterase inhibition were observed in one volunteer at the high dose (0.10 mg/kg). This individual reported having a "runny nose, blurred vision, and a feeling of faintness" after 9 days of treatment. Dosing of all individuals at the high dose was terminated after 9 days on test, apparently due to these clinical signs of toxicity and marked cholinesterase inhibition (see discussion of cholinesterase inhibition below).

Clinical chemistry and hematology were unremarkable. Although a slight elevation in serum glucose was observed in all groups (including the controls) compared to baseline values this is probably due to blood samples being taken soon after the consumption of a meal.

A clear depression of plasma cholinesterase was observed at the high dose level (0.10 mg/kg) with the group mean value for the group decreasing to 1.7 umoles acetate/min/ml from a mean baseline value of 4.75 (a decrease of 64%) on the nineth day of treatment. After day 9, treatment ceased and a gradual recovery was observed with ChE values equaling baseline values by day 25 of the recovery period.

At the next lowest dose level, 0.03 mg/kg, an equivocal depression of plasma ChE was observed with the mean value decreasing to 3.4 umoles acetate/min/ml from a mean baseline value of 4.7. Although this represents a decrease of 28%, the small number subjects (4) and the great amount of variation from one measurement to another precludes the determinations that 0.03 mg/kg is an effect level. Treatment at this level continued for 20 days compared to 9 days at the 0.10 mg/kg dose level.

No compound related effect on RBC cholinesterase could be associated with chlorpyrifos administration at any dose level although it is noted that the sensitivity of the study to detect an effect on RBC ChE is limited by the small numbers of subjects and the variability in the assay.

No compound related effect of any form was observed at 0.014 mg/kg/day and no effect was observed on RBC cholinesterase at any dose level.

Discussion:

The clinical signs reported at the high dose level of this study conform to expected signs of generalized toxicity resulting from an anti-AChE agent (Koelle, 1975). The runny nose and blurred vision may be considered muscarinic effects and the "faintless" is considered to be a nicotinic effect. Plasma cholinesterase at the high dose was inhibited 64% compared to baseline values and although an equivocal depression of plasma ChE was observed at the mid dose level (0.03 mg/kg), this could not be clearly classified as a treatment-related effect. The LEL for plasma ChE inhibition and clinical signs of toxicity is 0.10 mg/kg and the NOEL appears to be 0.03 mg/kg in this study.

Core-Classification: Supplementary Data. Only males were tested and the number of subjects (4 per dose level) limits the sensitivity of the test.

Koelle, G.B. Anticholinesterase Agents, in "The Pharmacological Basis of Therapeutics", L.S. Goodman and A. Gilman, eds. Macmillan Publishing Co., Inc., New York, 1975.