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

006861

MEMORANDUM

AUG 23 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Request to Convene Toxicology Branch RfD/ADI Workgroup to Consider Re-evaluation of the RfD/ADI for Acephate

FROM: Krystyna K. Locke, Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Krystyna K. Locke 8/22/88

TO: Reto Engler, Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769C)

THRU: Edwin Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Budd 8/23/88

Tox. Chem. No.: 2A

Prior to 1986, the ADI for acephate was 0.025 mg/kg/day. In 1986, the Toxicology Branch (TB) RfD/ADI Workgroup re-evaluated this ADI and changed it to a Provisional ADI (PADI) of 0.0003 mg/kg/day. This substantial lowering of the ADI/PADI has now resulted in the TMRC exceeding many fold the PADI. In addition, data from a recently submitted 90-day rat study indicates the PADI would be further lowered to 0.0001 mg/kg/day if the same criteria were applied to this new study as were applied to the earlier 28-month rat study on which the PADI is presently based.

In response to this dilemma, the registrant of acephate, Chevron Chemical Company[1], met with TB in May of this year to discuss issues relating to the RfD/ADI. Shortly after the meeting, Chevron submitted a Position Document formally presenting their viewpoint and supporting documentation with respect to the issue of cholinesterase (ChE) inhibition and determination of the RfD/ADI for acephate. In essence, Chevron concluded that the rat is an inappropriate model to study ChE depression by acephate and since valid human data are available,

[1]Chevron Chemical Company and Sumitomo Chemical Company have recently formed a Joint Venture Company, Valent U.S.A. Valent has applied to the EPA for a company number and, when assigned, Valent will secure its own registration for acephate and other products.

Reviewed by: Krystyna K. Locke, Toxicologist
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd, Section Head
Section II, Tox. Branch (TS-769C)

# DATA EVALUATION REPORT

STUDY TYPE: Subchronic Oral: Cholinesterase Inhibition Tests (Human)

TOX. CHEM. NO.: 2 A

MRID NO.: 00015160

TEST MATERIAL: Mixtures of Technical Acephate (Orthene) and Technical Methamidophos (Monitor); purity not stated

SYNONYMS: RE 12420 (Acephate) and RE 9006 (Monitor)

STUDY NUMBER(S): IBT No. 636-02498

SPONSOR: Chevron Chemical Company

TESTING FACILITY: Industrial BIO-TEST Laboratories, Inc., Northbrook, Ill.

NOTE: This IBT study has been validated and classified as Supplementary data. See memorandum dated 10/21/80 (attached) from Gary J. Burin to Janet Auerbach.

TITLE OF REPORT: A Study of the Effects of Orthene and Monitor on Plasma and Erythrocyte Cholinesterase Activity in Human Subjects During Subacute Oral Administration.

AUTHOR(S): Garofalo, M.

REPORT ISSUED: March 7, 1973

CONCLUSIONS: Plasma cholinesterase (ChE) activity was inhibited as follows:

| Test Material Combination Monitor:Orthene | NOEL (mg/kg/day) | Sex | LEL (mg/kg/day) |
|---|---|---|---|
| 1:4 | 0.1 | M + F | 0.2 |
| 1:9 | 0.2 | M | 0.3 |
| | 0.3 | F | 0.4 |

Erythrocyte ChE activity was not inhibited. Hematology, blood chemistry and general health of the subjects were unaffected. Depressed plasma ChE activities returned to the pretest values during the 7-day recovery period.

Unsupervised weekend dosing, no record of food intake and too few subjects per test group constitute weak points in this study.

CLASSIFICATION OF STUDY: Acceptable as Core-Supplementary data.

EXPERIMENTAL PROCEDURES:

Seven male and seven female volunteers, 21-48 years old and weighing 54.5-122.1 kg, were given mixtures of RE-9006 (Monitor) and RE-12420 (Orthene) in two ratios, 1:4 or 1:9 (Monitor:Orthene). The group receiving the 1:9 ratio (3 males and 3 females) was given the following levels of the mixture (mg/kg/day): 0.1, 0.2, 0.3 and 0.4. The group receiving the 1:4 ratio (2 males and 2 females) was given only the 0.1 and 0.2 mg/kg/day levels. Each group was given increasing levels of the test materials until a significant inhibition of cholinesterase activity occurred, at which time administration was discontinued. Each dose was administered for a maximum of 21 days. The inhibition of cholinesterase activity was considered significant when it "was greater than two standard deviations below mean pretest activity for two consecutive bleedings."

The test material was administered as solutions in corn oil. The daily dose was administered via gelatin capsule in 3 equally divided doses (9:00 a.m., at noon and at 5:00 p.m.). The controls (2 males and 2 females) received gelatin capsules containing corn oil. The Monday through Friday dosing was supervised because the subjects had to report to the laboratory for their capsules. The weekend dosing was done by the individuals at home. The subjects did not know whether they were receiving test material or corn oil.

The following parameters were studied: plasma and erythrocyte ChE activities, hematology (hemoglobin, RBC count, hematocrit, and total and differential leucocyte count) and blood chemistry (bilirubin, total protein, glucose, BUN, SAP, SGPT and SGOT). The cholinesterase activities were determined[1] 5 times during the 2-week pretreatment period, 5-6 times during the treatment and once or twice during the recovery period. The hematology studies were conducted on day 6 before treatment and at the end of each treatment period. The subjects were instructed to report immediately any abnormal symptoms which occurred during the study.

[1]Levine, J. B., Scheidt, R. A., and Nelson, V., "An Automated Micro Determination of Serum Cholinesterase," Automation in Analytical Chemistry, Technicon Symposia, pp. 582-585. 1965.



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RESULTS:

Plasma ChE activities were inhibited significantly in the 1:4 and the 1:9 (Monitor:Orthene) groups. The inhibition in the 1:4 group was first noted at the 0.2 mg/kg/day level after 16 days of dosing and occurred in all subjects studied. The depression was greater than 2 standard deviations below mean pretest activity for two consecutive determinations.

The first significant inhibition in the 1:9 group was observed at the 0.3 mg/kg/day level after 21 days of dosing and only in the male subjects. At the 0.4 mg/kg/day level, 2 out of 3 female subjects tested exhibited a significant ChE depression after 10 days of dosing. All inhibited ChE activities returned to the pretreatment levels during the 7-day recovery periods.

Dosing human subjects with graded levels of the Monitor:Orthene mixtures for a total of 37 to 73 days had no effect on the erythrocyte ChF activity, hematology, blood chemistry, blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor, and finger tremor.

The pretest ChE activities in the erythrocytes were about the same in male and female subjects. However, nearly all plasma ChE activities in the females were about one-half of those reported for the males.

ACEPHATE TOX R 006861

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