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

AUG 18 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: NOEL for Baygon (Propoxur) in a 2-year rat chronic feeding study; comparison with a human volunteer study.

TO: Reto Engler, Ph.D., Chief
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THROUGH: Marcia van Gemert, Ph.D., Section Head
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and

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M. van Gemert 8/14/86
H. Farber 8/15/86

Background:

The question has arisen as to whether a slight (maximum 3.8%), but statistically significant (primarily during the first 20 weeks), mean body weight depression in male rats fed 200 ppm Baygon in their diet over a 2-year period was a toxicological effect of the test material. In a previous review (B. Backus, January 1985) it was stated that it was, and that a NOEL was therefore not observed. This is a reassessment of that statement, as well as a review of a human volunteer study from the literature.

Comments and Conclusions:

1. Baygon is a cholinesterase inhibitor, and females are usually more susceptible than males to the acute effects of pesticides of this type. However, mean body weights of 200 ppm females generally were within 2-3 grams of the corresponding control value for weighings during the first 40 weeks of the study. After that period, 200 ppm females actually tended to have slightly higher mean body weights than their controls (although differences were never statistically significant).

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2. Significant differences between mean weights of 200 ppm males and their controls occurred almost exclusively in the first 20 weeks of the study, during a period when males in the 200 ppm group had a slightly (statistically not significant) lower mean food consumption than their controls, suggesting the possibility that the 200 ppm Baygon diet was less palatable than the regular diet. It is emphasized that, other than the equivocal weight depression, there was no other possible indication of toxicity.
3. From the above it is concluded that the mean body weight depression in 200 ppm males observed in the study was equivocal, and that 200 ppm was a toxicological NOEL.
4. In a report titled "Toxicity of Carbamates for Mammals" (Vandekar, Plestina & Wilhelm, 1971) an oral dose of 135 mg of Propoxur (1.5 mg/kg to a 90-kg human male) resulted in pronounced symptoms (pronounced nausea, vomiting, profuse sweating, a rise in blood pressure from 135/90 to 175/95) of cholinesterase inhibition 30-45 minutes after ingestion. There was a maximum of 73% RBC ChE activity depression 15 minutes after ingestion. According to the graph, RBC ChE had essentially recovered to normal at 2 hrs.

Subsequently, an unspecified number of volunteers took 5 doses of either 0.15 or 0.2 mg/kg at half-hourly intervals. In each case a "symptomless depression" was observed in RBC ChE, to about 60% of normal.

A dose of 1.5 mg/kg, while causing symptoms in a human volunteer when ingested all at once, was essentially "detoxified" (RBC ChE activity returned to normal) in 2 hours (according to an accompanying graph). At this rate of RBC ChE activity recovery a cumulative dose of 1.5 mg Baygon/kg over a 24 hr period would probably not have resulted in any evident symptoms; this would be equivalent to 60 ppm in the diet. However, 1.5 mg/kg x 12 (number of 2-hr periods in 24 hrs) = 18 mg/kg (720 ppm) would probably have caused symptoms.

It is noted that 0.36 mg/kg is reported as having caused "short-lasting" effects with recovery of RBC ChE within 3 hours (note that detoxification of 1.5 mg/kg took place in approximately 2 hours; this may indicate individual variation or some other factors at work).

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Section III, Tox. Branch (TS-769C)

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Section III, Tox. Branch (TS-769C) *M. van Gemert 8.14.86*

DATA EVALUATION REPORT

STUDY TYPE: Oral Toxicity - human TOX. CHEM. NO: 508

ACCESSION NUMBER: MRID NO.:

TEST MATERIAL: Baygon (Propoxur)

STUDY NUMBER: (Bull. Wld. Hlth Org. 1971, 44, 241-249)

TESTING FACILITY: Institute for Medical Research
Yugoslav Academy of Sciences
Zagreb, Yugoslavia

TITLE OF REPORT: Toxicity of Carbamates for Mammals

AUTHOR(S): Vandekar, M., Plestina, R. and Wilhelm, K.

REPORT ISSUED: 1971

STUDY CLASSIFICATION: Core Supplementary Data

SUMMARY AND CONCLUSIONS:

1. Non-lethal effects (blurred vision, nausea, sweating, increased blood pressure, and vomiting) occurred in a 42-year old 90 kg male subject who ingested 1.5 mg/kg Propoxur. Effects were most pronounced in the period from 30 to 45 minutes after ingestion. An RBC ChE inhibition of 73% was observed 15 minutes after ingestion. Two hours after ingestion of the Propoxur the subject was feeling well enough to eat a regular meal, and, according to the accompanying graph, RBC ChE activity had essentially returned to normal.
2. A single dose of 0.36 mg/kg caused a rapid fall in RBC ChE activity (to 57% of normal), with transient stomach discomfort, blurred vision, moderate facial redness and sweating. RBC ChE recovered to normal activity levels within 3 hours.
3. There were usually no symptoms accompanying drops in RBC ChE activity to 60% of normal.

Materials and Methods:

Propoxur (95% pure) was orally administered at 1.5 mg/kg to a 90 kg 42-year-old male subject, 2 hours after breakfast. Cholinesterase measurements were made "spectrophotometrically" 4 times during the first hour, twice during the second, and at 3, 7.5 and 36(?-poor copy) hrs after dosage. Also, measurements were made of the excretion of phenol derivatives in the urine.

Additional studies were done in which an unspecified number of human volunteers received 5 doses of either 0.15 mg/kg or 0.20 mg/kg propoxur at half-hour intervals, with measurements being made of RBC ChE activity, and 0.36 mg/kg was administered as a single dose.

Results:

Single dose of 1.5 mg/kg:

RBC ChE dropped to 27% of normal activity 15 minutes after ingestion. Subsequently, discomfort (pressure in the head), blurred vision and nausea developed, and the blood pressure went from 135/90 to 175/95. Symptoms were most pronounced 30-45 minutes after ingestion, and included pronounced nausea, repeated vomiting and profuse sweating. There was essentially complete recovery (both in terms of symptoms and RBC ChE) 2 hrs after ingestion. There was a pronounced increase in excretion of phenol derivatives in the subject's urine in the 5 hours following ingestion, which then dropped back to normal:

Time after ingestion (minutes)	volume of urine (ml)	Concentration of phenol derivatives in urine (ug/ml)
Pre-exposure	55	20.0
110	108	177.5
285	107	195.6
430	250	37.8
515	196	21.3
515 to 1440	790	24.3

Multiple (5X) Doses of 0.15 or 0.2 mg/kg:

Transient depressions of RBC ChE activities to about 60% of normal were observed, with no symptoms. RBC ChE activities recovered within 2-3 hours of the last dose.

Single Dose of 0.36 mg/kg:

There was a rapid (within 10 minutes) drop in RBC ChE activity

to 57% of normal, along with transient (5 minutes) stomach discomfort, blurred vision, moderate facial redness and sweating. The RBC ChE recovered to its normal level in 3 hours.

Discussion:

The primary value of the information in this published article is that it seems to correlate, certainly within an order of magnitude, with what has been observed in animal studies. It also indicates that a sudden drop in RBC ChE activity to slightly less than 60% of normal is associated with appearance of symptoms of cholinesterase inhibition (there is no evidence that this sudden drop in RBC ChE is responsible for the symptoms; these probably occur as a direct result of inhibition of brain and/or neuromuscular ChE).

A dose of 1.5 mg/kg, while causing symptoms in a human volunteer when ingested all at once, was essentially detoxified (RBC ChE activity returned to normal) in 2 hours. At this rate of recovery a cumulative dose of 1.5 mg/kg Baygon/kg over a 24 hr period would probably not have resulted in any evident symptoms; this would be equivalent to 60 ppm in the human diet. However, 1.5 mg/kg x 12 (number of 2-hr periods in 24 hrs) = 18 mg/kg (720 ppm) may have caused symptoms.

Again, it is emphasized that these values must be taken as "correct within an order of magnitude." The number of human volunteers in this study was very low, and only males may have been tested.