CASWELL FILE

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

006609

FEB 25 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA File No.: 067501. Piperonyl butoxide: Review of metabolism and pharmacokinetic studies in rats.

TOX CHEM No.: 670
TOX PROJECT No.: 8-0271
Record No.: 209979

FROM: John Doherty John Doherty 2/19/88
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Geraldine Werdig
DATA-CALL-IN Program
Registration Division (TS-767)

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

Background

In a previous review by Toxicology Branch (TB, refer to review by J. Doherty dated September 25, 1987 for EPA File No. 067501) it was stated that the metabolic fate of piperonyl butoxide (PB) "be determined at least to the point that the major metabolites or those metabolites which may be considered terminal be identified as far as possible". In response to this review, a document entitled "Single and Repeat Oral Dose Pharmacokinetics and Distribution Studies of Piperonyl Butoxide-Final Report" has been submitted to TB by the DATA-CALL-IN unit with the instructions that TB "review the protocol and determine if it will be useful in resolving questions concerning the metabolic fate of Piperonyl Butoxide as requested in your review dated 9/25/87".

Toxicology Branch Response

1. The document submitted has been reviewed (refer to Data Evaluation Record attached) and TB has determined that since no attempts were made to identify the metabolites, the study will not satisfy TB's request to identify the major and/or terminal metabolites of PB.

   Additional data depicting the metabolic pathway of PB will have to be generated and submitted. The major metaboites and/or terminal metabolites should be identified as best as possible (refer to the September 25, 1987 memo for discussion).

2. The study submitted was determined to be SUPPLEMENTARY, although there were some important and useful data generated regarding the pharmacokinetics and tissue distribution of ^{14}C following a high dose (500 mg/kg) oral administration of PB. The study, however, utilized only the high dose level and only a single sex (males) were studied. A lower (tracer level) and females should also have been included.

006609

Reviewed By: J.D. Doherty 2/19/88
Section II, Toxicology Branch (TS-769C)
Secondary Reviewer: E.R. Budd 2/19/88
Section II, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: 85- Metabolism and Pharmacokinetics

Accession Nos.: 260122

TOX Chem No.: 670
MRID No.: None Provided

Test Material: [^{14}C] Piperonyl Butoxide (labeled in the [2-(2-butoxy-ethoxy)ethoxy]methyl side chain).

Synonyms: PB

Study Number: None provided

Sponsor: Piperonyl Butoxide Task Force

Testing Facility: Biological Test Center
2525 McGaw Avenue
Irvine, California

Title of Report: Single and Repeat Oral Dose Pharmacokinetics and Distribution Studies of Piperonyl Butoxide

Author: Sami Selim

Report Issued: October 18, 1985

Conclusions:

This study defines the peak blood levels, urinary and fecal excretion and tissue distribution of piperonyl butoxide (PB) in male rats following single and repeated oral administration of 500 mg/kg. PB is slowly absorbed from the GI tract and blood levels peak after 4 to 6 hours. Urinary and fecal excretion peaked between 12 to 24 and 24 to 48 hours, respectively. No evidence of specific tissue retention was presented.

Classification:

Core-SUPPLEMENTARY (Only males and a single dose level were studied. No attempts to identify the chemical structure of the metabolites were presented).

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

The Quality Assurance Officer was indicated as being Rod Patterson. No special quality assurance statement or history of inspections was provided with this report.

Review:

The objectives of this study were to obtain information on the absorption, distribution, and excretion of PB following both single and repeated oral administration to the rat. No attempts were made to determine the chemical structure of the metabolites.

The test materials used for this study were both unlabeled and ^{14}C labeled PB. The unlabeled material was described as being 100 percent PB "equivalent to minimum 80 percent (butylcarbityl)-6-propylpiperonyl)ether and 20 percent related compounds." The radioactive (^{14}C) material was synthetized by the Amersham Company, and was reported as having the specific activity of 3.4 mCi/mmol with a radiochemical purity of 95 to 96 percent.

Only male (CD) rats were used as the test animals and they were obtained from the Charles River Breeding Labs, Wilmington, "Delaware" (more probably they were from Wilmington, Massachusetts). On receipt at the laboratory they were young adults and weighed about 240 g.

The procedures used in this study consisted of counting aliquots of liquid samples (urine and blood). Tissues (about 100 mg) and feces samples were collected and the ^{14}C material was trapped in cocktail and transferred to counting vials. One set of preliminary experiments also determined the $^{14}CO_2$ expired by the rat.

The following is a brief description of the three experiments reported including the significant results.

1. Preliminary Experiments

This first study was designed to determine if ^{14}C-PB was metabolized by the rat to yield volatile (respired) $^{14}CO_2$. Four rats were dosed with 500 mg/kg of PB containing approximately 10 uCi of ^{14}C and placed into Roth metabolism cages for 24 hours. The rats were fasted 16 to 18 hours prior to dosing and for the first 4 hours after dosing. The air expired by the rats was trapped by bubbling through a mixture of 2:1 ethanolamine/cellusolve and this solution was counted for ^{14}C activity after 2, 6, and 24 hours.

The report states that no significant amounts of volatile ^{14}C were found in the CO_2 trap. Only 0.18 percent of the administered dose was reported as being recovered in the expired air. On this basis, the later definitive studies were conducted in open cages because metabolism of PB to CO_2 was determined not to be a significant route of degradation.

A second preliminary experiment was conducted in order to gain information regarding the pharmacokinetics of PB so that appropriate times for sacrifice and tissue distribution analysis could be selected for the main study. In this experiment, four rats were fasted and then dosed with 500 mg/kg of PB as above (containing ^{14}C PB) and blood samples were collected from the tail vein and analyzed for radioactivity at 1/4, 1/2, 3/4, 1, 2, 3, 4, 6, 12, and 24 hours later.

This study revealed that the plasma levels increased slowly such that maximum blood levels of ^{14}C activity were at 4 to 6 hours with lesser amounts being present at 12 and 24 hours. Since no measurements were made between 6 and 12 hours, TB notes that the blood level may have maintained its peak for most of the 4- to 12-hour period and possibly a few hours afterward. At 24 hours the blood was a little more than 1/2 of the peak level.

2. Single Oral Dose Studies

This aspect of the project was divided into two groups. The first group of four rats that were fasted prior to dosing was dosed with a single oral (gavage) dose of about 500 mg/kg containing 12.5 to 15.2 uCi of ^{14}C and the rats were housed individually in metal metabolism cages for separate and simultaneous collection of urine and feces. Urine and feces were collected at 4, 8, 12, and 24 hours and each succeeding 24-hour period for 7 days.

This experiment revealed that the radioactivity in the urine peaked at 12 to 24 hours and declined slowly until 72 hours when 1 percent or less of the excreted dose was being eliminated. Fecal excretion peaked at 24 to 48 hours and it declined slowly until between 120 to 144 hours when less than 1 percent of the excreted dose was being eliminated by this route.

The recovery data from this experiment indicated that, based on the means from the four rats, 37.43 ± 5.04 and 62.14 ± 8.97 percent radioactivity was recovered in the urine and feces, respectively. A total of 99.58 ± 6.91 percent total recovery was reported for the 168-hour (7-day) experiment.

The second aspect of the single oral dose study also involved dosing fasted rats with about 500 mg/kg of PB containing 13 to 15 uCi of ^{14}C labeled PB. The rats, four at each time interval, were sacrificed 1, 6, 24, and 48 hours and at 7 days.

Table 18 (photocopied from the study report) illustrates the average tissue recovery in ppm of PB at the different sacrifice times. It is noted that the fat, liver, prostate, muscle and kidney (based on the 48-hour sample time) retain the most radioactivity. After 7 days, most of the radioactivity has declined to < 12 ppm. (Note: The gastrointestinal organs all contained higher counts than the organs mentioned above but since the PB was administered by gavage, the GI system is not considered the same way as the internal organs by this reviewer.)

The significance of PB showing relatively moderately high concentrations in the prostate and seminal vesicles was not discussed but may relate to the high fat content of these tissues.

3. Repeated Oral Administration Study

In this study, a group of five rats was dosed via feeding such that they were to receive approximately 500 mg/kg/day of unlabeled PB for 13 days. On the 14th day, the rats were fasted and dosed by gavage with about 500 mg/kg/day of PB containing 9.4 to 9.8 uCi of ^{14}C. Urine and feces were collected for up to 7 days. After 7 days the rats were sacrificed and their tissues evaluated for ^{14}C content following combustion.

The urinary and fecal excretion patterns for the repeated dose study were essentially the same as for the single dose study. Recovery of the administered dose was 97.35 $\pm$ 5.90 percent with 43.45 $\pm$ 7.36 and 53.90 $\pm$ 5.93 percent being in the urine and feces, respectively.

Table 23 (photocopied from the study report) shows the tissue distribution of ^{14}C 7 days after administration of the test dose. The tissue distribution of isotope was essentially similar to the distribution following the single oral dose.

Conclusion:

This study is considered SUPPLEMENTARY. The study defines the pharmacokinetics of PB with respect to peak levels in the blood, urine, and fecal excretion and tissue distribution following single and repeated (14 days) doses of 500 mg/kg. No attempts were made to determine the structure of the metabolites. Another deficiency is that only male rats were used; current guidelines require that both sexes be used. This study assesses only the pharmacokinetics at 500 mg/kg. A second dose level (preferably a tracer level) should also have been used.

Piperonyl butoxide - Tox Review 006609

Page _____ is not included in this copy.

Pages 7 through 8 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
