

UNDATED

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Malathion: Metabolism Study in Sprague-Dawley Rats. Midwest
Research Institute. 1989. MRID 41367701. HED Doc No. 007791.

DATA EVALUATION RECORD

Study Type: Metabolism Study, Rats
OPP Guideline 85-1

P.C. Code: 057701

Tox. Chemical No.: 535

Test Material (purity): 14C-Malathion; (98% purity)

Synonyms O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate; O,O-dimethyl phosphorodithioate of diethyl mercaptosuccinate; diethyl mercaptosuccinate, S-ester with O,O-dimethyl phosphorodithioate; Cythion; AC6,601.

Citation: V. Reddy, T. Freeman and M. Cannon, 1989. Disposition and Metabolism of 14C-Labeled Malathion in Rats (Preliminary and Definitive Study). Midwest Research Institute. Study No. MRI 9354-B. December 20, 1989. Unpublished.
MRID 41367701.

Sponsor: Malathion Task Force

Executive Summary:

In a metabolism study in Sprague-Dawley rats, single doses of radiolabeled 14C-malathion (98% purity; SA = 90.0 uCi/mg) were administered by oral gavage to groups of 5 male and 5 female adult rats at dose levels of 40 mg/kg (low dose), 800 mg/kg (high dose) and 40 mg/kg following 15 days of daily oral gavage of non-radiolabeled malathion (94.6% purity) at a dose level of 40 mg/kg/day. The rats were then placed in metabolism cages and urine and feces were collected for 72 hours. Radioactivity in urine and feces was determined at 4, 8, 12, 24, 48 and 72 hours after dosing. In a preliminary study, it was determined that less than 1% of the radioactivity in similarly treated animals was eliminated in expired air. At 72 hours, the animals were sacrificed and major organs/tissues (including GI tract plus contents and residual carcass) were collected, weighed and analyzed for radioactivity. Whole blood, plasma and erythrocytes were also analyzed for radioactivity. In addition, individual and pooled urine and fecal samples were analyzed for biotransformation products (i.e. malathion and metabolites) at 0-24 hours and 24-48 hours after dosing.

More than 90% of the radioactivity in the 40 mg/kg low dose was excreted within 72 hours with most excretion occurring in the first 24 hours and considerably less occurring during the remainder of the 72 hour period. Approximately 80-90% of the radioactivity in the administered dose was excreted in the urine

with females excreting slightly more than males in the urine. Only minor differences in urine/fecal excretion ratios were observed between animals given 40 mg/kg (low dose), 800 mg/kg (high dose) and 40 mg/kg after 15 previous daily doses of malathion. At 72 hours, the highest concentration of radioactivity was observed in the liver, but less than 0.3% of the administered radioactivity was present in that organ. Radioactivity did not bioaccumulate in any of the organs/tissues analyzed. Although 8 radiolabeled metabolites were observed in urine, greater than 80% of the radioactivity in urine was represented by the diacid (DCA) and monoacid (MCA) metabolites. The remaining radiolabeled metabolites were identified as components of "peak A" and "peak B". It was determined that between 4 and 6% of the administered dose was converted to malaoxon, the active cholinesterase inhibiting metabolite of malathion.

This study is **ACCEPTABLE** and **SATISFIES** guideline 85-1 for a general metabolism study in rats.

TB997: MALATH14.087

DATA EVALUATION RECORD

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OPP Guideline 85-1

P.C. Code: 057701

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TB997:MALATH14.087



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

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CASWELL FILE

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Malathion, Metabolism Study in Rats

TO: J. Edwards, PM-74
Registration Division (H7505C)

FROM: *[Signature]* 2/15/90
Robert P. Lendzian Ph.D.
Senior Pharmacologist
SACB, HED (H7509C)

THROUGH: Albin Kocialski Ph.D.
Head
Registration Standards and Special Review Section

ABK 2/28/90

Reto Engler Ph.D.
Chief
Science Analysis and Coordination Branch

Compound; Malathion

Tox Chem #535

MRID #413677-01

Registration #241-208

Registrant; Malathion Task
Force

Tox Project #0-0606

Action Requested

Review the following study;

Disposition and metabolism of ¹⁴C-labeled malathion in rats (preliminary and definitive study), V. Reddy, T. Freeman & M. Cannon, Midwest Research Institute, MRI Project No. 9354-B, Dec 20, 1989, MRID 413677-01

Conclusion

Guideline study

¹⁴C-labeled malathion was dose orally at 40 and 800 mg/kg and 40 mg/kg following 14 daily doses of 40mg/kg/day. 90+ percent of the dose was excreted in 72 hrs with 80-90% excreted in the urine. Females excreted slightly more in the urine than males. Between 4 and 6 % of the dose was converted to the active inhibitor, malaaxon.

Attachment
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Gardner

Compound MalathionCitation

Disposition and metabolism of ^{14}C -labeled malathion in rats (preliminary and definitive study), V. Reddy, T. Freeman & M. Cannon, Midwest Research Institute, MRI Project No. 9354-B, Dec 20, 1989, MRID 413677-01

Reviewed by *[Signature]* 1/27/90
Robert P. Zandzian Ph.D.
Senior Pharmacologist

Core Classification GuidelineConclusion

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MaterialsMalathion, CAS 121-75-5

O,O-Dimethyl-S-(1,2-dicarboxyethyl)phosphorodithioate
Deep Brown to yellow liquid

Nonlabeled

Product No. W 60930-6038

Purity 94.6%

^{14}C -Labeled malathion (labeled in the carbons of the dicarboxy)

Lot No. C4

Purity 98%

specific activity 90.0 uCi/mg

Adult male and female Sprague-Dawley (Cr1:CD BR) rats 7 to 10 weeks old from Charles River

Experimental Design

Doses were administered orally by gavage in a volume of 4 ml corn oil/kg as follows:

Study	Sex	No. of Animals	Nominal Dose (mg/kg)	Actual Dose _a (mg/kg/)
Preliminary	M	1	40	36.9
	F	1	40	37.4
	M	1	800	796.4
	F	1	800	765.9

<u>Study</u>	<u>Sex</u>	<u>No. of Animals</u>	<u>Nominal Dose (mg/kg)</u>	<u>Actual Dose^a (mg/kg/)</u>
Definitive	M	5	40	36.4
Single Dose	F	5	40	37.1
	M	5	800	755.3
	F	5	800	751.8
Multiple _b Dose	M	5	40	35.1
	F	5	40	36.3

a. mean of dosed animals.

b. following 15 daily single doses of 40mg/kg/day.

Doses were prepared by adding sufficient quantity of ¹⁴C malathion and sufficient nonlabeled malathion to corn oil to produce final concentrations of 10 or 200 mg/ml for the 40 and 800 mg/kg dose groups, respectively. Prepared dosing solutions were analyzed and actual doses calculated.

Preliminary study.

Animals were dosed as above and placed individually in metabolism cages. Urine, feces and expired air were collected and analyzed for radioactivity at 4, 8, 12, 24, 48 and 72 hours after dosing. "At 72 hours, the animals were anesthetized with ether and esanguinated by withdrawal of blood from the abdominal aorta."

Definitive study.

Animals were dosed as above and placed in individual metabolism cages. "Following the administration of the radio-labeled dose (low, high and multiple dose groups), urine and feces were collected and measured for radioactivity content at 4, 8, 12, 24, 48 and 72 hr. At 72 h, all animals were killed as described previously for tissue sampling." The following tissues were collected weighed and analyzed;

- | | | |
|---------|----------|------------------------|
| Liver | Splee | Muscle (thigh) |
| Kidneys | Adrenals | Fat (retroperitoneal) |
| Lungs | Testes | Bone (femur) |
| Brain | Uterus | Skin |
| Heart | Ovaries | GI tract plus contents |
| | | Residual Carcass |

Whole blood, plasma and RBC were analyzed.

Individual and pooled urine and fecal samples from the dosed animals were analyzed for biotransformation (malathion and metabolites).

Results

Preliminary study.

Dose excretion, as percent of applied dose, was as follows;

Route	40 mg/kg		800 mg/kg	
	Male	Female	Male	Female
Expired	0.92	0.33	0.44	0.32
Air				
Urine	93.92	93.81	83.38	89.31
Feces	8.59	4.05	14.55	15.25
Total	103.43	98.19	98.37	104.88

Definitive study.

Excretion (urinary, fecal and total) are presented as percent of dose per collection period and cumulative percent of dose in Table 1 (males) and 2 (females) from the report. Data are summarized as follows;

Route	40 mg/kg		800 mg/kg		40 mg/kg X 15	
	Male	Female	Male	Female	Male	Female
Urine	83.83	88.03	76.17	85.24	84.56	88.36
Feces	10.95	5.95	13.68	6.61	6.81	5.81
Total	94.78	93.97	89.85	91.85	91.38	94.17

Dose distribution in blood, tissues and excreta is presented, as ug Equivalants/g tissue and percent of dose, in Table 3 (males) and 4 (females) from the report. The highest concentration and percent of dose was observed in the liver. No indication of bioaccumulation was observed.

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21-0

Metabolic profiles, as percent of total radioactivity, are presented in Table 5 (urine) and 6 (feces). Of the eight radiolabeled metabolites identified, the diacid (DCA) and mono acids (MCA) represented greater than 80 % of the recovered radioactivity. The remaining 5 radiolabeled metabolites were identified in peaks A and B. Based on the metabolites of malathion that were identified, a possible metabolic pathway is presented in Figure 6 from the report. This figure has been modified as noted below.

Discussion

Malathion must be converted to malaoxon in order to inhibit cholinesterase. Therefore, determination of the percent of malathion converted into malaoxon is critical.

Figure 6 shows the conversion, by oxidation, of malathion to malaoxon but the figure, as presented in the report, omits a critical metabolic step which is indicative of the inactivation of malaoxon and/or its reaction with cholinesterase. Malaoxon can be inactivated by removal of the 2-mercaptosuccinic acid group or malaoxon can react with cholinesterase a step which also releases 2-mercaptosuccinic acid. However, 2-mercaptosuccinic acid was not identified as a metabolite but rather its metabolites 2-mercaptosuccinic acid disulfide and fumaric acid. This metabolic process is shown in the modifications of Figure 6 which indicate malaoxon metabolism. The maximum possible conversion of malathion to malaoxon is the total of malaoxon, 2-mercaptosuccinic acid disulfide and fumaric acid, given as minor metabolites constituting between 4 and 6 percent of the dose of malathion. Maximum cholinesterase reacted enzyme is given as the total of 2-mercaptosuccinic acid disulfide and fumaric acid, between 2 and 4 percent of the dose of malathion.

This conclusion is supported by data on the intraperitoneal LD50s of malathion and malaoxon in the rat. The respective values are 900 and 25 mg/kg, indicative of 2.8% malathion converting to malaoxon and reacting with the enzyme.

INRSD 41367701
DEC # 17

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Pages 10 through 18 are not included in this copy.

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- Identity of product inert impurities.
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