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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES
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MEMORANDUM

SUBJECT: Larvin®; Thiodicarb:Acetamide Metabolism

TO: Jay Ellenberger
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and

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and

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The Toxicology Branch has reviewed reports on the metabolism, toxicity and oncogenicity of Larvin® in animals. The attached summary is intended to provide an overview of toxicokinetic and exposure issues with respect to Larvin, methomyl, and the metabolite acetamide. Base and incremental risks associated with existing and proposed uses of Larvin are presented.

cc: A. Barton
W. Burnam
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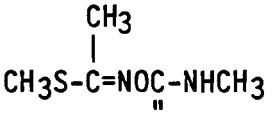
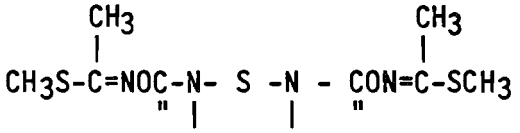
METABOLISM (RAT, COW):

The disposition of acetyl-1-^{14}C thiodicarb has been studied in rats[1,2] given single oral doses of 16 or 40 mg/kg and in a lactating cow[3] given 7.02 mg/kg. In addition, a study was conducted to determine the disposition of ^{14}C-thiodicarb in lactating cows (2/group) dosed with the test material in capsules at levels equivalent to dietary concentrations of 0.1, 10, 30 and 100 ppm for 21 days.[4]

Thiodicarb essentially consists of two methomyl moieties joined at their amino nitrogen atoms by sulfur. Thiodicarb is rapidly converted to methomyl in the rat stomach; over 30% of an oral dose of 16 mg thiodicarb per kg body weight was converted to methomyl in the gut within 15 minutes. Only 40% of the radioactivity in an oral dose was found in the rat gut at 15 minutes, indicating that the compound had been rapidly absorbed. Approximately 26% of the dose was found in other body fractions, and the remainder (34%) was apparently lost as volatiles.[1]



METHOMYL



THIODICARB

It is apparent that metabolites of a single dose of thiodicarb in the cow are excreted in different proportions than in the rat, although this reviewer has found no indication that there are any substantial differences in the metabolic pathways involved. During the initial 3-day period following administration of radiolabeled thiodicarb[1] (16 mg/kg) or methomyl[5] (4 mg/kg) in rats, 31-32% of the applied dose was found in the urine. Only 5% of a dose of thiodicarb (7.02 mg/kg) administered to a cow was excreted in the urine during the same period.[3] In rats, approximately 40-50% of the dose was recovered as CO_2 and/or acetonitrile from respired gases during a 72-hour period, while the cow similarly eliminated 66% of the applied dose. The CO_2:acetonitrile ratio in respired air was 4- to 16-fold higher in the cow than in the rat. This reviewer believes that the higher CO_2:acetonitrile ratios in cows may represent a species specific tendency toward reduced formation of the anti-methomyl stereoisomer. Huhtanen and Dorough[6] showed that, in the rat, the more stable syn isomer is metabolized predominantly to carbon dioxide, while partial conversion from the syn to the anti isomer leads primarily to the formation of acetonitrile (see Figure 1). Although not addressed by the registrant, it appears possible that there is a species-related difference in conversion of syn-methomyl to anti-methomyl, and/or excretion of acetonitrile vs. metabolic hydrolysis to acetamide. An alternative explanation of the stoichiometric differences in carbon dioxide and acetonitrile formation may be that the preparation administered to rats differed from that given to cows, with respect to impurities (i.e., formation of anti-methomyl directly from stereoisomers of syn,syn-thiodicarb).

Harvey et al[7] reported that, in rats given oral doses (approximately 4-7 mg/kg) of radiolabeled methomyl, the radioactivity was rapidly eliminated in the ratio of 1 part CO_2:2 parts acetonitrile:1 part urinary metabolites. A trace amount of radioactivity was recovered in the feces, and this was attributed to contamination with urine. Andrawes[8] reported that oral administration of radiolabeled acetonitrile to rats resulted in elimination of 65% of the applied dose in expired air, with less than 1% expired as $^{14}CO_2$. In a similar study, however,

Huhtanen and Dorough[6] found that 9.1% of a dose of acetonitrile in rats was eliminated as CO_2 in respiratory gases.

Two lactating Holstein cows/group were given approximately 0.004, 0.4, 1.4 or 4 mg ^{14}C-thiodicarb per kg body weight daily for 21 days.[4] Milk and urine were collected twice daily, and blood and feces were collected at 3-4 day intervals. One cow at each dosage level was sacrificed 12 hours after the last treatment and tissues (liver, kidney, lung, spleen, heart, brain, ovary, udder, tongue, foreleg muscle, hindleg muscle, neck muscle and omental fat) were collected for analysis. The remaining 4 cows (1 at each dosage level) were kept for an additional 7 days after termination of treatment. During this post-treatment phase, milk and urine were collected twice daily as before, and blood and feces were collected daily. The same tissues were collected from these animals 7 days post-treatment. The radioactivity found in all samples (i.e., tissue, milk, blood, urine and feces) was dose dependent. The predominant end products of thiodicarb catabolism were found to be acetonitrile, acetamide and carbon dioxide. The concentration of acetonitrile in milk approached peak levels within 7 days in all dose groups. The acetonitrile levels appeared to remain nearly constant through the rest of the 21-day treatment period, then declined sharply during the 7-day post-treatment phase. Acetamide, which is believed to be produced by hydrolysis of acetonitrile, was found in trace amounts (<0.01 ppm) in milk at the highest feeding level. Approximately 24% of the aqueous extractable urinary radioactivity was identified as acetamide. Following 21 days of treatment, tissue levels of ^{14}C residues were highest in liver and lowest in adipose tissues. Seven days after termination of dosing, radioactivity levels were lower in all tissues except liver.

In the cow given a single dose (7.02 mg/kg), 66, 11.4, 5.0 and 4.6% of the administered radioactivity was eliminated during 72 hours post-treatment in respired air, feces, urine and milk, respectively, while 10.1% was retained in the tissues.

OTHER TOXICOLOGICAL CONSIDERATIONS:

Larvin Technical was not found to be oncogenic in rats (CORE Minimum; Carnegie-Mellon, Report #43-18; 3/24/80; EPA Accession #070764, Document #001820, 003706 and 003707) or mice (CORE Minimum; Carnegie-Mellon, Report #43-10; 1/25/80; EPA Accession #070764, Document #001820, 003706, 003707) when administered in-diet for 2 years at doses up to and including 10 mg/kg/day (the highest dose level tested). In each study, the NOEL for systemic toxicity was 3 mg/kg/day and the LEL was 10 mg/kg/day. At the 10 mg/kg level, the test material caused decreased body weight in rats and increased mortality in mice.

Larvin Technical was not teratogenic when administered via oral gavage in mice at levels up to and including 200 mg/kg (CORE Minimum; IRDC, Report #369-031; 2/26/81; EPA Accession #09923, Document #001996, 001997) or in rats at levels up to and including 100 mg/kg (CORE Minimum; Carnegie-Mellon, Report #42-48; 6/1/79; EPA Document #003694), the highest respective doses tested.

Results of a 3-generation reproduction study in rats (CORE Minimum, Document #001820/CORE Supplementary, Document #003706; Carnegie-Mellon, Report #42-64; 7/2/79; EPA Accession #070764) showed no adverse reproductive effect at 10 mg/kg/day, the highest dose level tested.

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Larvin Technical was found negative for mutagenicity in a series of six CORE Acceptable studies, i.e., a rat dominant lethal test (Carnegie-Mellon, Report #42-65; 7/2/79; EPA Document #003706), an Ames test (LBI, Report #20838; 4/78; EPA Document #003706), a mouse micronucleus test (Pharmakon, Report #PH-309-UC001-79; 5/22/79; EPA Document #003706), a reverse mutation assay in Saccharomyces cerevisiae (Pharmakon, Report #PH-303-UC-001-79; 6/1/79; EPA Document #003706), mitotic crossover in S. cerevisiae (Pharmakon, Report #PH-302-UC-001-79; 6/1/79; EPA Document #003706) and a primary DNA damage test (Pharmakon, Report #PH-305-AM-002-79; 5/14/79;EPA Document #003706). In an additional study, however, the test material was found to have produced increased mitotic gene conversion in S. cerevisiae (Pharmakon, Report #PH-304-UC-001-79; 6/1/79; EPA Document #003706).

DIETARY EXPOSURE, RISK CONSIDERATIONS

The estimated dietary exposure levels for existing uses of methomyl and Larvin are 1.54×10^{-2} and 7.15×10^{-4} mg/kg/day, respectively. The incremental exposure for the proposed uses of Larvin on cotton and soybeans would be 3.85×10^{-5} mg/kg/day.

In a previous memo, B. Litt (Statistician, Toxicology Branch) derived a Q_1^* value of 3.07×10^{-3} $(mg/kg/day)^{-1}$ for acetamide. Assuming 100% conversion of Larvin (m.w. 363) to acetamide (m.w. 59), at a molar ratio of 1:2, maximum acetamide exposure would be 32.5%(i.e., [2 x 59]/363) that of Larvin, or 2.32×10^{-4} mg/kg/day for existing uses and an additional 1.25×10^{-5} mg/kg/day for proposed uses on cotton and soybeans. Likewise, 100% conversion of methomyl (m.w. 165) to acetamide at a molar ratio of 1:1 would result in maximum acetamide exposure at a level 35.8% that of methomyl, or 5.51×10^{-3} mg/kg/day for existing uses. Thus, the upper 95% confidence limit of lifetime risk based on acetamide for all existing uses of methomyl is 4.73×10^{-5} and for existing uses of Larvin is 2.20×10^{-6}. The incremental risk for the proposed uses of Larvin on cotton and soybeans would be 1.18×10^{-7}.

SUMMARY/RECOMMENDATIONS:

The parent compound, thiodicarb (Larvin), was found to be non-oncogenic in rats and mice. It was non-mutagenic in the Ames test and in 5 of 6 additional assays. This compound, however, is metabolised in mammals to form acetamide. Because acetamide is suspected of being an animal carcinogen[9], it is necessary to quantify the amount of acetamide exposure that could result from ingestion of thiodicarb residues. The purity of the radiolabeled thiodicarb which was used in the metabolism studies (i.e., 98%) was greater than that of the technical material (approximately 96%). For risk assessment purposes, the registrant (Union Carbide Corporation) should provide sufficient data to show that the presence of stereoisomers of syn, syn-thiodicarb will be limited to a specified level which may be used to quantitate maximum acetamide formation in animals exposed to Larvin.

Exposure estimates for Larvin and methomyl residues (separately and combined), as well as calculated levels of resulting acetamide exposure and risk, are presented in Table 1. The Toxicology Branch has calculated the upper 95% confidence limit of lifetime risk for all existing methomyl and Larvin uses to be 4.95×10^{-5}.

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TABLE 1.

Compound	Dietary Exposure (mg/kg/day) Existing Uses	Incremental (Cotton/Soybeans)	Total
Methomyl	1.54×10^{-2}	---	1.54×10^{-2}
Larvin	7.15×10^{-4}	3.85×10^{-5}	7.54×10^{-4}
Methomyl+Larvin	1.61×10^{-2}	3.85×10^{-5}	1.62×10^{-2}
Parent Compound	**Acetamide Exposure (mg/kg/day)**		
Methomyl	5.51×10^{-3}	---	5.51×10^{-3}
Larvin	2.32×10^{-4}	1.25×10^{-5}	2.45×10^{-4}
Methomyl+Larvin	5.74×10^{-3}	1.25×10^{-5}	5.76×10^{-3}
Parent Compound	**Lifetime Risk Based on Acetamide Exposure**		
Methomyl	4.73×10^{-5}	---	4.73×10^{-5}
Larvin	2.20×10^{-6}	1.18×10^{-7}	2.32×10^{-6}
Methomyl+Larvin	4.94×10^{-5}	1.18×10^{-7}	4.95×10^{-5}

This reviewer considers it prudent at this time to assume 100% conversion of dietary residues of Larvin to acetamide unless additional data are provided by the registrant to allow for a reduced estimate of human exposure to acetamide. Based on the results of several overlapping studies performed in rats, the registrant has developed a diagram of the metabolic pathway (Figure 1) and has shown that the maximum level of conversion of Larvin to acetamide is approximately 53:1 on a weight-to-weight basis. Supporting data and calculations are presented in Appendix 1. This reviewer recommends that the above ratio be used as a conservative estimate of Larvin:acetamide conversion for revised risk calculation purposes if the following provisions are met:

- The Toxicology Branch requests substantiation from the registrant that technical grade Larvin contains only the syn,syn isomeric form of thiodicarb, or that the differences between the isomeric purity of Larvin technical and that of the thiodicarb used in the metabolism studies would not introduce changes in the calculated ratio of thiodicarb conversion to acetamide.

- In order to more fully assess the potential species-specific metabolic conversion of thiodicarb to acetamide, additional studies should be performed in species other than the rat and cow. The monkey is recommended as one such additional species.

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REFERENCES

1) Andrawes, N., College, P. and Bailey, R., "Short term fate of orally administered UC 51762 in the rat," UCC Project Report, File No. 23509.

2) Andrawes, N. and Bailey, R., "Metabolism of acetyl-1-^{14}C Larvin in the rat," UCC Project Report, File No. 26925, 10/12/79.

3) Khasawinah, A., and College, P., "Fate of a single oral dose of ^{14}C-acetyl UC 51762 in a lactating cow -- metabolism into natural products," UCC Project Report, File No. 25257, 7/10/78.

4) Feung, C., College, P. and Chancey, E., "Studies on the disposition of ^{14}C-thiodicarb in lactating cows," UCC Project Report, File No. 27350, 2/13/80.

5) Andrawes, N. and Bailey, R., "Metabolism of acetyl-1-^{14}C methomyl in the rat," UCC Project Report, File No. 26946, 10/18/79.

6) Huhtanen, K. and Dorough, H., "Isomerization and Beckmann rearrangement reactions in the metabolism of methomyl in rats," Pest. Biochem. Physiol. 6, 571-583 (1976).

7) Harvey, J., Jelinek, A. and Sherman, H., "Metabolism of methomyl in the rat," J. Agr. Food Chem. 21, 769-775 (1973).

8) Andrawes, N., "Acetonitrile metabolism in the rat," UCC Project Report, File No. 32291, 12/5/83.

9) Weisburger, J., Yamamoto, R., Glass, R. and Frankel, H., "Prevention by arginine glutamate of the carcinogenicity of acetamide in rats," Toxicol. Appl. Pharmacol. 14, 163-175 (1969).

Thiodicarb toxicology review

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