

6-22-94

090301.001

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Methomyl [S-methyl-N-
((methylcarbamoyl)oxy)-thioacetamidate]

CASRN. 16752-77-5
EPA Chem. Code: 090301
Caswell No. 549 C

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Fungicide-Herbicide Branch
Registration Division (7505C)

Lois Rossi, Chief
Re-registration Branch
Special Review and Re-registration Division (7508W)

The Health Effects Division RfD/Peer Review Committee met on April 13, 1994 to discuss and evaluate the existing and recently submitted toxicology data in support of Methomyl re-registration and to re-assess the Reference Dose (RfD) for this chemical. The Committee was asked also to determine whether the acetamide, a relatively weak carcinogen and a minor metabolite of Methomyl (found in goats, cows, poultry, rats and monkeys but not in plants) constitutes a potential carcinogenic hazard as a result of consuming methomyl and/or acetamide residues.

Material available for review included data evaluation records for a chronic toxicity/oncogenicity study in rats (83-1a and -2a or 83-5), a carcinogenicity study in mice (83-2b), a long-term feeding study in dogs (83-1b), developmental toxicity studies in rats (83-3a) and rabbits (83-3b), a reproductive toxicity study in rats (83-4) and a subchronic feeding study in dogs (82-1b).

The Committee agreed, as per the request of the respective branch, to postpone the discussion on all aspects except the acetamide metabolite issue. The Committee concluded that the ingestion of anticipated levels of Methomyl and acetamide in the diet should not represent a significant carcinogenic hazard to the consuming public based on the following: 1) the conversion rate of methomyl to acetamide is low (approximately 2-3%), therefore, residue levels of acetamide should be low, 2) carcinogenicity studies with methomyl were negative in two rodent species under the testing conditions, 3) the product is comprised of 98.7% syn-isomer and 0.092 anti-isomer, syn-isomer must be converted to anti-isomer before acetamide is formed, and 4) acetamide induced liver tumors in rats only when administered at very high dosages, i. e. more than 1000 mg/kg/day. Acetamide was evaluated by the HED Carcinogenicity Peer Review Committee (CPRC) and classified as a "Group C" but it was recommended that no low dose extrapolation model was to be used for risk assessment.

The Committee recommended that the RfD for this chemical remain unchanged until further evaluation of toxicology data. The RfD for this chemical was first determined by the Health Effects Division RfD Committee on March 21, 1986 and verified by the Agency RfD Work Group on April 22, 1986. At that time, the RfD was based on a two-year feeding study in dogs with a no-observable effect level (NOEL) of 2.5 mg/kg/day. Histopathological changes in the kidney and spleen were observed at 10.00 mg/kg/day. An uncertainty factor of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.025 mg/kg/day. It should be noted that this chemical has been discussed in the WHO/FAO joint meeting on pesticide residues (JMPR) in 1989. An acceptable daily intake (ADI) of 0.03 has been established. The JMPR considered the following studies to be critical in the ADI determination: 1) a mouse chronic feeding study with a NOEL of 8.7 mg/kg/day, 2) a rat chronic feeding study with a NOEL of 2.5 mg/kg/day, and 3) a dog chronic feeding study with a NOEL of 3.1 mg/kg/day.

A. Individuals in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Marcia Van Gemert

Henry Spencer

Roger Gardner

James Rowe

William Sette

George Ghali

Rick Whiting

2. Scientific Reviewer(s) (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Clark Swentzel

3. Others:

L. Kutney, S. Williams, Melba Morrow, D. McCall and K. Dearfield of HED as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Clark Swentzel
Alan Levy
James Kariya
RfD File
Caswell File