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

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JUL 26 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RFD/Peer Review Report for Sulfosate

FROM: Rick J. Whiting
Health Effects Division (7509C)

Rick J. Whiting 7/26/94

TO: Robert Taylor
Fungicide-Herbicide Branch
Registration Division (7505C)

Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Division (7508W)

It has been brought to my attention that the RfD/Peer Review meeting date stated in the recently distributed RfD/Peer Report for Sulfosate (dated July 21, 1994) is incorrect. The correct meeting date is March 10, 1994.

Please replace your RfD/Peer Review Report with the new attached report. Thank you.

cc: Richard Scmitt
Kerry Dearfield
Karl Baetcke
Roger Gardner
Pam Hurley
James Kariya
RfD and Caswell Files

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MEMORANDUM

SUBJECT: RfD/Peer Review Report of Sulfosate [N-phosphonomethyl-glycinetrimethylsulfonium salt].

CASRN. 81591-81-3
EPA Chem. Code: 128501
Caswell No. 893C

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (7509C)

Rick J. Whitney 7/26/94 for

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

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

The Health Effects Division RfD/Peer Review Committee met on March 10, 1994 to discuss and evaluate the existing toxicology data in support of Sulfosate re-registration and to re-assess the Reference Dose (RfD) for this chemical.

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

The Committee considered the chronic toxicity studies in rats (83-1a, MRID No. 40214007, 41209905) and dogs (83-1b, MRID 40214005, 41209901) to be acceptable and the data evaluation records (HED Doc. No. 006542, 008368; 006337, 008368) to be adequate. The Committee questioned the biological significance of the body weight decrease observed in the rat study and considered it to be secondary to the reported reduction in food consumption. The organ weight changes observed at the high dose was also

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attributed to the decrease in body weight. The Committee also questioned the biological significance of the lactic dehydrogenase changes at the lowest dose level tested in this study. The Committee, therefore, recommended revising the no-observable effect level (NOEL) from 100 ppm, the lowest dose, to 1000 ppm, the highest dose level tested. The Committee questioned the biological significance of the lactic dehydrogenase changes at the highest dose level (50 mg/kg/day) in the dog study. However, when the findings of this study were viewed in light of the 90-day study in dogs, the Committee felt that the NOEL was appropriately set in the long-term dog study at 10 mg/kg/day based on salivation and emesis.

The highest dose tested in the rat carcinogenicity study (83-2a, MRID No. 40214007, 41209905) was considered to be inadequate for carcinogenicity testing. Limited body weight decreases observed in this study (8-10% in males and 8-9% in females) were not considered severe enough to indicate that the animals in this study were tested at a sufficiently high dose level for an adequate negative carcinogenicity testing in rats. The decrease in body weights was proportional, and thus, might be attributable to reduction in food consumption. However, the Committee determined that the high dose level tested in this study was approaching, at least, one half of what might have been considered an adequate dose level for carcinogenicity testing. This assessment was based on toxic effects observed in the subchronic and reproductive toxicity studies in rats at higher doses. Furthermore, there was no indication of any carcinogenic response to warrant repeat of the study. The Committee considered the carcinogenicity study in mice (83-2b, MRID No. 40214005, 41209901) to be acceptable. The Committee determined that the highest dose level tested in the mouse study might have been excessively high. The data evaluation records for the two carcinogenicity studies (HED Doc. No. 006542, 008368; 006337, 008368) were considered to be adequate. The treatment did not alter the spontaneous tumor profile in either species under the testing conditions. On the basis of these two studies, the chemical was classified as a "Group E".

The Committee considered the developmental toxicity studies in rats (83-3a, MRID No. 00126618, 00132183, 00155387) and rabbits (83-3b, MRID No. 00155526), and the reproductive toxicity study in rats (MRID No. 00154273, 00162487) to be acceptable and the data evaluation records for these studies (HED Doc. No. 003578, 004585, 005584; 005450; 005173, 005690) to be adequate. The Committee determined that the death of three dams in the high dose group in the rat developmental toxicity study might have been compcund-related. The Committee disagreed with the statement in the rabbit developmental toxicity study that no developmental toxicity was observed at 100 mg/kg/day, the highest dose tested, based on the following: 1) there was a reduction in the number of live fetuses/doe for the seven surviving rabbits at the highest dose tested, 2) four of the high dose rabbits aborted their litter, apparently all of the fetuses were dead in those litters (if

included in the calculations, there would be a statistically significant decrease in live fetuses/doe and postimplantation loss, and 3) having only seven litters does not give a sufficiently high number of animals to support the conclusion that no developmental toxicity has occurred, particularly at the high dose. In the two-generation reproduction study, the Committee concluded that there was a statistically significant depression of multiple absolute and sometimes relative organ weights in both generations (thymus, heart, kidney, liver) at the mid- and high-dose which appear to be biologically significant due to the minimal changes observed in body weight, body weight gain and food efficiency. Therefore, the paternal NOEL would appear to be the Lowest dose tested of 150 ppm (6.1 and 8 mg/kg/day in males and females, respectively).

The Committee recommended that a neurotoxicity battery including acute neurotoxicity (81-8), subchronic neurotoxicity (82-7), and delayed neurotoxicity (81-7) be submitted with subsequent requirement of a developmental neurotoxicity study if the outcome of these studies warrant such data. This recommendation was based on the following observations: 1) increased incidence of white matter and nerve-root degeneration in lumbar region of spinal cord of male mice at the high dose tested (8000 ppm) and a compound-related increase in sciatic nerve degeneration at all dose levels in male mice in the two-year mouse study, 2) the observation of occasional sciatic nerve degeneration in male and female rats administered sulfosate topically at the rate of 1 gm/kg for three weeks, 3) the observation of hydrocephalus after one year of oral administration of sulfosate in dogs, and 4) the observation of lateral ventricle dilation in female dogs fed test compound at the rate of 50 mg/kg/day for three months. The Committee was informed that the neurotoxicity studies have already been requested and received by Agency. When the data evaluation records (DERs) are finalized, the Committee will review the DERs and determine whether a developmental neurotoxicity study should be required.

The Committee recommended that an RfD for this chemical be established based on a chronic feeding study in dogs with a no-observable effect level of 10 mg/kg/day. Emesis was observed at the next higher dose level of 50 mg/kg/day (see discussion of the dog study, above). An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.1 mg/kg/day.** It should be noted that this chemical has not been reviewed by the joint Committee meeting of the WHO/FAO on pesticide residues (JMPR).

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A. Individuals in Attendance

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

William Burnam

Marcia Van Gemert

Karl Baetcke

Henry Spencer

Roger Gardner

James Rowe

Esther Rinde

William Sette

Stephen Dapson

George Ghali

Rick Whiting

2. Peer Review Committee Members and associates in absentia (Signature indicates concurrence with the peer review unless otherwise stated).

Reto Engler

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

Roger Gardner

Pam Hurley

William Dykstra

4. Others:

T. McMahon, John Tice, and K. Locke of HED as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
James Kariya
RfD and Caswell Files
Roger Gardner
Pam Hurley

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B. Material Reviewed

Material available for review included data evaluation records for a chronic toxicity/carcinogenicity study in rats (883-1a and -2a or 83-5), a carcinogenicity study in mice (83-2b), a chronic toxicity study in dogs (83-1b), a multi-generation reproductive toxicity study in rats, two developmental toxicity studies in rats (83-1a), two developmental toxicity studies in rabbits (83-3b), and short-term toxicity studies in rats and dogs (82-1a and -1b).

1. Pavkov, K. L. and Wyand, S. (1987). Two-year chronic toxicity and oncogenicity dietary study with SC-0224 in rats. MRID No. 40214007, 41209905, HED Doc. No. 006542, 008368. Classification: Guideline data. This study satisfies data requirement 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Pavkov, K. L. and Turnier, J. C. (1987). Two-year chronic toxicity and oncogenicity dietary study with SC-0224 in mice. MRID No. 40214006, 41209907, HED Doc. No. 006542, 008368. Classification: Guideline data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Knapp, H. F. and Thomassen, R. W. (1987). One-year chronic oral toxicity study with SC-0224 in beagle dogs. MRID No. 40214005, 41209901, HED Doc. No. 006337, 008368. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Minor, J. L., et al (1984). SC-0224: Two-generation reproduction study in rats. MRID No. 00154273, 00162487, HED Doc. No. 005173, 005690. Classification: Guideline data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Downs, J. R. and Minor, J. L. (1982). A teratology study in CD rats with SC-0224. MRID No. 00126618, 00132183, 00155387, HED Doc. No. 003578, 004585, 005584. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Downs, J. R. and Minor, J. L. (1983). A teratology study in New Zealand rabbits with SC-0224. MRID No. 00155526, HED Doc. No. 005450. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

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