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MEMORANDUM

SUBJECT: RfD/Peer Review Report of Sulprofos (Bolstar); O-Ethyl-O-[4-(methylthio)phenyl] S-propylphosphorodithoate.

CASRN: 35400-43-2
EPA Chem. Code: 111501
Caswell No.: 453AA

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

THRU: William Burnam
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Dennis Edwards, PM 19
Fungicide-Herbicide Branch
Registration Division (7505C)

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

The Health Effects Division-RfD/Peer Review Committee met on January 25, 1995 to discuss and evaluate the existing and/or recently submitted toxicology data in support of Sulprophos reregistration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a and -2a)**, 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 and rabbits **(83-3a and -3b)**, acute and subchronic neurotoxicity studies in rats **(81-7 and 82-6)**, an acute neurotoxicity study in hens **(81-5)**, a 21-day dermal toxicity study in rabbits **(82-2)** and a battery of mutagenicity studies **(84-2)**.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, MRID No. 00085496) to be acceptable and the data evaluation record for this study (HED Doc. No. 000000) to be adequate. Minor revisions were recommended to the data evaluation record of this study.

The NOEL/LOEL for both plasma and red blood cell cholinesterase inhibition were considered to be 0.3 and 3 mg/kg/day, respectively. The Committee determined that marginal plasma cholinesterase inhibition was observed at the lowest dose level tested in females. However, the Committee determined also that the lowest dose level tested was at or near the NOEL for plasma cholinesterase inhibition. The NOEL/LOEL for brain cholinesterase inhibition and other systemic toxicity endpoints were considered to be 3 and 12.5 mg/kg/day, respectively. Some of the histopathological effects observed, when compared to the historical control incidences, were considered to be age-related rather than treatment-related. Changes in organ weights also were observed, but were not accompanied by histopathological changes.

The Committee examined the chronic toxicity phase of the mouse carcinogenicity study (83-2b, MRID No. 00085484). In this study there appeared to be increased incidences and severity of retinal dystrophy in the high dose males and females indicative of potential ocular effects. The Committee recommended minor revisions to the data evaluation record of this study (HED Doc. No. 000000). Statistical analysis of the findings were recommended by the Committee. The NOEL/LOEL for plasma and red blood cell cholinesterase inhibition were considered to be 0.38 and 3.8 mg/kg/day, respectively, in both males and females. The NOEL for brain cholinesterase inhibition in males and females were considered to be 60 and 30 mg/kg/day for males and females, respectively. Pancreatic atrophy in males, tracheitis and chronic laryngitis in both sexes, fatty changes of the liver in males and chronic peribronchiolitis of the lungs in females were observed at increased incidences in treated groups in comparison to controls, but were considered to be age related. The NOEL for systemic toxicity was considered to be 60 mg/kg/day, the highest dose level tested.

The Committee considered the two-year feeding toxicity study in dogs (83-1b, MRID No. 00085485) to be acceptable and the data evaluation record (HED Doc. No. 000000) to be adequate. The NOEL/LOEL for plasma, red blood cell and brain cholinesterase inhibition were considered to be 0.25 and 2.5 mg/kg/day, respectively. The NOEL for systemic toxicity was initially determined by the scientific reviewer to be 3.75 mg/kg/day, the highest dose level tested. However, the Committee requested that a determination of some indication of potential ocular toxicity at this level had occurred which could substantiate the apparent

increase in retinal dystrophy in mice. The Committee recommended further evaluation of this parameter. A further evaluation following the RfD Committee meeting of the histopathological findings in the eyes of both sexes of dogs did not reveal any treatment related effects at the high dose of 3.75 mg/kg/day. Therefore, the increased incidence of retinal dystrophy in mice was not substantiated in the 2-year dog study.

There were no subchronic toxicity studies in rats (82-1a) or dogs (82-1b) available for review by the Committee.

B. Carcinogenicity:

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (83-2a, MRID No. 00085496) to be acceptable and the data evaluation record (HED Doc. No. 000000) to be adequate. The highest dose level tested was considered to be adequate for carcinogenicity testing based on body weight gain decrease observed at week 13 and on cholinesterase inhibition. The most frequently observed tumors in this study were pancreatic islet cell adenomas and adrenal pheochromocytomas, both appeared to be slightly increased in males. However, the increase did not attain a statistically significant level in the pair-wise comparison with the concurrent controls and was not statistically significant in the trend analysis test. The incidences of these two tumors were also within the historical control range for these types of tumors in this strain of rat.

The Committee considered the mouse carcinogenicity study (83-2b, MRID No. 00085484) to be acceptable and the data evaluation record (HED Doc. No. 000000) to be adequate. The highest dose level tested was considered to be adequate for carcinogenicity testing based on cholinesterase inhibition. The Committee determined that the treatment did not alter the spontaneous tumor profile in this strain of mice.

The Committee recommended that the chemical be classified as a **"Group E"**, evidence of non-carcinogenicity for humans, i.e. the chemical is **not likely** to be carcinogenic to humans via relevant routes of exposure.

This weight of the evidence judgment is largely based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies. It should be noted, however, that designation of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

C. Reproductive and Developmental Toxicity:

The Committee considered the 2-generation reproductive

toxicity study in rats (83-4, MRID No. 00085496) to be acceptable and the data evaluation record (HED Doc. No. 000000) to be adequate. The Committee considered the finding of this study to be consistent with effects observed in the rat chronic study. The parental systemic toxicity NOEL/LOEL were considered to be 60 ppm (3 mg/kg/day) and 120 ppm (6 mg/kg/day), respectively. The NOEL/LOEL for plasma and red blood cell cholinesterase inhibition in both males and females and for brain cholinesterase inhibition in females were considered to be 3 and 6 mg/kg/day, respectively. The reproductive toxicity NOEL was considered to be 6 mg/kg/day, the highest dose level tested.

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 00094676) to be acceptable and the data evaluation record (HED Doc. No. 000000) to be adequate. The study was initially classified by the scientific reviewer as Core-supplementary data because of reporting deficiencies. The Committee determined that the reporting deficiencies (litter data for skeletal variations) had no impact on the overall conclusion of the study with respect to developmental toxicity. Therefore, the Committee recommended that the study be elevated to Core-minimum data. According to the data evaluation record, the NOEL/LOEL for both maternal and developmental toxicity were considered to be 10 and 30 mg/kg/day. The LOEL for maternal toxicity was based on frequent clinical signs included exophthalmos, gritting of teeth, clonic muscle spasms, ventrolâteral position, kyphosis, and tremors) observed at 30 mg/kg/day, the highest dose level tested. The LOEL for developmental toxicity was based on increased in the number of fetuses with incompletely ossified sternebrae No. 6 in the 30 mg/kg/day dose group, the highest dose level tested.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 00043791) to be supplementary, and the data evaluation record for this study (HED Doc. No. 000000) to be adequate. The study was initially classified by the scientific reviewer as invalid. The Committee determined that a new developmental toxicity study in rabbits will not be needed at this time. It is the Committee's position that the data from the rat and the rabbit studies, when considered together, provide adequate assessment of the developmental toxic potential for this chemical. Therefore, the requirements for developmental toxicity testing were considered satisfied. According to the data evaluation record, the NOEL/LOEL for maternal and developmental toxicity were considered to be 3 and 10 mg/kg/day, respectively. Maternal toxicity was manifested as diarrhea and decrease food and water consumption, drowsiness, salivation, proneness and increased mortality at 10 mg/kg/day and higher dose levels. The study report noted that the stomach and intestines of does which died during the study were essentially empty. The developmental toxicity NOEL/LOEL were considered to be 10 and 30 mg/kg/day, based on decreased implantations. However, due to maternal deaths at this dose (5 out

of 13 does died), only 36 fetuses were examined in 7 litters.

D. Mutagenicity:

The Committee considered the following mutagenicity studies to be acceptable:

1) Salmonella typhimurium reverse gene mutation assay (Accession/MRID No. 246539): The test is negative in all strains up to an insoluble level of 12,500 μg/plate in the presence or absence of metabolic activation (+/-S9).

2) Chinese hamster ovary (CHO)/HGPRT forward gene mutation assay (Accession/ MRID No. 252875): The test is negative up to an insoluble level of 100 μg/mL in the presence or absence of metabolic activation (+/-S9).

3) Mouse micronucleus assay (Accession/MRID No. 262404): The test is negative in NMRI mice up to 200 mg/kg administered once daily for 2 consecutive days by oral gavage. Although there was no overt toxicity or bone marrow cytotoxicity, radiolabeled bolstar was detected in bone marrow at a level that was directly proportional to the oral dose administered in a rat metabolism study (MRID NO. 42557401).

4) Mouse dominant lethal assay (Accession/MRID No. 00043790): The test is negative in NMRI male mice at a single dose of 200 mg/kg administered by oral gavage. Although there was no overt toxicity or adverse effects on reproductive or dominant lethal parameters, radiolabeled bolstar was detected in testes in a rat metabolism study (MRID NO. 42557401).

5) Escherichia coli pol $A^{+/-}$ liquid suspension DNA damage/repair assay (Accession/MRID No. 253989): The test is negative up to a precipitating dose of 100 μg/mL in the presence or absence of (+/-S9).

The Committee overall concluded that the acceptable studies satisfy both the new and Pre-1991 mutagenicity initial testing battery guidelines.

Based on the available toxicology data, there is no concern for mutagenicity at this time.

E. Acute and Subchronic Neurotoxicity:

The Committee considered the acute delayed neurotoxicity study in the hen (81-5, MRID No. 00043782) to be acceptable and the data evaluation record (HED Doc. No. 000000) to be adequate. The study is negative.

The Committee considered the acute neurotoxicity study in rats

(81-7, MRID 42737001) to be acceptable and the data evaluation record (HED Doc. No. 010823) to be adequate. The LOEL for plasma and red blood cell cholinesterase inhibition was considered 29 mg/kg/day, the lowest dose level tested. The neurotoxicity LOEL was considered to be 29 mg/kg/day, based on ataxia and tremor in females and muscle fasciculation in males. The NOEL for cholinesterase inhibition and neurotoxicity was not established in this study.

The Committee considered the subchronic neurotoxicity study in rats (82-6, MRID 42893301) to be acceptable and the data evaluation record (HED Doc. No. 010843) to be adequate. The Committee considered that the red blood cell cholinesterase inhibition (13%) observed in males at 0.5 mg/kg/day, lowest dose tested, and the brain cholinesterase inhibition (14%) observed also in males at 2.5 mg/kg to be toxicologically significant.

F. Reference Dose (RfD):

The Committee recommended that the RfD for this chemical remain unchanged. The RfD for this chemical was established based on the long-term (one-year) oral toxicity study in dogs with a NOEL of 0.25 mg/kg/day. At the next higher dose level of 2.5 mg/kg/day, plasma, red blood cell and brain cholinesterase inhibition was observed. An uncertainty factor (UF) of 100 was applied to account for both the interspecies extrapolation and the intraspecies variability. On this basis, the RfD was calculated to be 0.0025 mg/kg/day.

It should be noted that this chemical has not been reviewed by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR), and an Acceptable Daily Intake (ADI) has not been established.

G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/QA Peer Review Committee), George Ghali (Manager, RfD/QA Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief, TB II), Stephen Dapson, Roger Gardner, Nancy McCarrol and Henry Spencer. In attendance also was Kit Farwell of HED as an observer.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

William Dykstra _____

Roger Gardner _____

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke _____

CC: Stephanie Irene
Debra Edwards
Albin Kocialski
Karl Baetcke
William Dykstra
Roger Gardner
Karen Whitby
Paula Deschamp
Beth Doyle
Amal Mahfouz (OW)
RfD File
Caswell File

H. Material Reviewed:

1. Lamb, D. W. and Hoss, H. E. (1978). Bolstar (BAY NTN 9306) Chronic Feeding Study on Rats. MRID No. 00085496. HED Doc. No. 000000. Classification: Core minimum data. This study satisfies data requirement 83-5 (83-1a and 83-2a) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity and carcinogenicity testing in rats.

2. Lamb, D. W. and Hoss, H. H. (1978). Bolstar (BAY NTM 9306) Chronic Feeding Study on Mice. MRID No. 00085484, HED Doc. No. 000000. Classification: Core minimum data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Lamb, D. W. and Hoss, H. E. (1978). (Bolstar (BAY NYN 9306): Two Year Feeding Study on Beagle Dogs. MRID No. 00085485, HED Doc. No. 000000. 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. Reno, F. R. (1977). A Three-Generation Study in Rates With NTN 9306. MRID No. 00085495, HED Doc. No. 000000. Classification: Core minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Becher, H. (1981). Embroyotoxicity and Teratogenicity Study in Rats with NTN 9306. MRID No. 00094676, HED Doc. No. 000000. Classification: Core minimum data as upgraded by the RfD Committee. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Machemer, L. (1975). NTN 9306: Studies for Embryotoxic and Teratogenic Effects on Rabbits Folowing Oral Administration. MRID No. 00043791, HED Doc. No. 000000. Classification: Core supplementary data as upgraded by the RfD Committee from Core invalid. This study by itself does not satisfy data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits. However, when considered with the rat developmental toxicity study (MRID No. 00094676 above), the requirement for developmental toxicity testing are considered satisfied.

7. Sheets, L. P. and Hamilton, B. F. (1993). A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Sulprofos (Bolstar) in Fischer 344. MRID No. 42893301, HED Doc. No. 010843. Classification: Core Guideline data. This study satisfies data requirement 82-6 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity

testing in rats.

8. Sheets, L. P. (1993). An Acute Oral Neurotoxicity Screening Study with Technical Grade Sulprofos (Bolstar) in Rats. MRID No. 42737001, HED Doc. No. 010823. Classification: Core minimum data. This study satisfies data requirement 81-7 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in rats.

9. Thyssen, J. and Siegmund, F. (1975). NTN 9306: Neurotoxicity Study on Hens. MRID No. 00043782, HED Doc. No. 000000. Classification: Core minimum data. This study satisfies data requirement 81-5 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in hens.

10. Lamb, D. W. (1975). BAY NTN 9306 6 (Emulsifiable) Subacute Dermal Toxicity to Rabbits. MRID No.: 00043798, HED Doc. No. 000000. Classification: Core supplementary data (according to the DER). This study was not discussed by the Committee.

11. Herbold, Dr. B. (1980). NTN 9306 Sulprofos: Salmonella/Microsome Test for Determination of Point Mutations. MRID No. 00096608, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

12. Van Goethem, D. L. (1983). Evaluation of Bolstar in the CHO/HGPRT Assay. MRID No. 252875, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

13. Herbold, Dr. B. (1982). Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect with Sulprofos. MRID No. 00158534, HED Doc. No. 000000. Classification: Acceptable This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

14. Machemer, L. (1975). NTN 9306; Dominant Lethal Study on Male Mice to Test for Mutagenic Effects. MRID No. 00043790, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

15. Van Goethem, D. L. (1983). Evaluation of Bolstar in the E. coli POL A+/A - DNA Repair Liquid Suspension Assay. MRID No. 00141224, HED Doc. No. 86013 Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.