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

MAY 16 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Sodium Omadine [Sodium 2-pyridinethiol-1-oxide, or sodium pyrithione].

CASRN. 15922-78-8
EPA Chem. Code: 088004
Caswell No. 790A

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

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

TO: Marshall Swindell, PM 31
Antimicrobial Branch
Registration Division (7505C)

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

The Health Effects Division-RfD/Peer Review Committee met on February 2, and again on March 30, 1995 to discuss and evaluate the existing and recently submitted toxicology data in support of Sodium Omadine re-registration and to assess a Reference Dose (RfD) for this chemical.

The chemical is proposed for use as an antimicrobial agent to inhibit the growth of bacteria and fungi mainly in metal working fluids (constitutes 99% of sales), adhesives, plastic products, resin emulsions, floor finishes, laundry rinse additives, laundry detergents, carpet cleaners, links, and specialty industrial products.

Material available for review consisted of data evaluation records (DERs) for a combined chronic toxicity/carcinogenicity study in rats **(83-1a and -2a or 83-5)**, a dermal carcinogenicity study in mice **(83-2b)**, a one-year oral toxicity study in monkeys **(83-1b)**, two-generation reproductive toxicity study in rats **(83-4)**, a dermal developmental toxicity study in rabbit **(83-3a)**, a subchronic oral/neurotoxicity study in rats **(82-1 and -7)**, a subchronic dermal toxicity study in rats **(82-3)**, a subchronic

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inhalation [illegible] ·4) and a battery of mutagenicity [illegible] or gene mutations (84-2a), structural ch[illegible] (84-2b), and other genotoxic effects (84-4).

A. Chronic and Subc[illegible]xicity:

The Committee considered [illegible]e chronic toxicity studies in rats (83-1a, MRID No. 42100901) and Cynomolgus monkeys (83-1b, MRID No. 41178101) to be acceptable and the data evaluation records for these studies (HED Doc. No. 011532) to be adequate. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the studies. No revisions were recommended to the data evaluation records.

The Committee considered the subchronic dermal toxicity study in rats (82-3, MRID No. 40936201) to be acceptable and the data evaluation record (HED Doc. No. 011532) to be adequate. There was no evidence of dose-related dermal irritation. Dose-related clinical signs were observed in the high-dose females including emaciation, hunched posture, stiff hindlimbs, incoordination, and tremors. Body weight gain was significantly affected in females of the high dose group. Dose-related gross histopathological changes of the hindlimb skeletal muscle were observed in the mid-dose females and in high-dose males and females. In addition, degeneration of sciatic nerve fibers accompanied by demyelination and minimal atrophy in the paravertebral muscle were seen in the high dose-females.

The Committee considered the subchronic inhalation toxicity study in rats (82-4, MRID No. 41178201) to be acceptable and the data evaluation record (HED Doc. No. 011532) to be adequate. Females of the high dose group exhibited signs of hindlimb dysfunction, histopathological skeletal muscle degeneration and decrease body weight gain. Males did not show any signs of treatment-related effects.

The Committee considered the subchronic oral toxicity phase (82-1a, MRID No. 40756901) of the combined subchronic oral and neurotoxicity toxicity study in rats to be acceptable for the subchronic oral toxicity phase of the study and the data evaluation record (HED Doc. No. 011532) addressing the subchronic portion of the study to be adequate. The neurotoxicity phase of the study (82-7, MRID No. 40756901) was considered to be unacceptable. Several deficiencies were noted in both the conduct and reporting of the study (see neurotoxicity below).

B. Neurotoxicity:

The Committee considered the neurotoxicity phase (82-7) of the combined subchronic oral toxicity/neurotoxicity study in rats (82-7, MRID No. 40756901) to be unacceptable. The Committee noted

that effects on motor activity, grip strength, neuropathological changes, and other observations were not reported.

While explicit neurotoxicity studies were not required, data from the existing studies provided evidence of neurotoxic effects. Although the existing studies would not satisfy current neurotoxicity guidelines, explicit neurotoxicity studies were not recommended due to limited anticipated exposure for uses subject to FIFRA. However, it was recommended that the effects seen early in the subchronic study in rats be considered relative to any acute exposure risk assessment.

C. Carcinogenicity:

These types of studies are not usually required for the registration of non-food use chemicals except under certain circumstance. . In the case of this chemical, these studies were deemed necessary under the Registration Standard of 1986 because of the high exposure.

The Committee considered the carcinogenicity study in rats (83-2a, MRID No. 42100901) to be acceptable and the data evaluation record (HED Doc. No. 011532) to be adequate. The Committee considered the dose levels tested in this study to be adequate for carcinogenicity testing in this strain of rat. The highest dose tested was associated with a significant decrease in mean body weight (and body weight gain) in females throughout the study, a marked increase in nerve fiber degeneration in the sciatic nerve and in the spinal cord and an increased incidence of retinal atrophy in both sexes. The treatment did not alter the spontaneous tumor profile in this strain of rat under the testing conditions.

The Committee considered the dermal carcinogenicity study in mice (83-2b, MRID No. 42100801) to be inadequate. The chemical was not tested at a sufficiently high dose level. The highest dose level tested, 40 mg/kg/day, was associated with an increase in the incidence of epidermal hyperplasia at the application site in males and females but no systemic toxicity of any kind was observed in either sex. The Committee determined that mice could have tolerated higher dose levels. The data evaluation record of this study stated that "the maximum dose, 40 mg/kg/day, was chosen based on the results of a 13-week dermal toxicity study in rats, and a 28-day dermal toxicity study in mice. The Committee dismissed this rationale of dose selection for the following reasons: 1) extrapolation of data from the rat to the mouse in this case would be in appropriate given the obvious species-specific sensitivity of the rat, and 2) the 28-days dermal toxicity study in mice has never been submitted to the Agency and was not available for review by the Committee to ascertain the registrant's claim. The scientific reviewer indicated that the 28-day dermal toxicity study in mice was only mentioned in the report of the main carcinogenicity study in mice. In the meeting of February 2, the Committee, tentatively,

down-graded the mouse carcinogenicity study from Core-minimum data to a Core-supplementary status until the 28-day dermal toxicity study is made available to the Committee for review. Generally, the Committee concluded that the treatment was not associated with increased incidences of neoplasms at any site under the testing conditions.

In the meeting of March 30, and after reviewing the 28-day dermal toxicity study in mice, the Committee upheld its earlier position and reiterated its recommendation regarding the mouse carcinogenicity study. The Committee concluded that the 28-day dermal toxicity study did not address the Committee's concern and did not provide any support for the dose selection for the mouse carcinogenicity study. The Committee, therefore, concluded that the classification of the carcinogenicity study in mice should remain as Core-supplementary data. The Committee also indicated that a new study would not be required at this time as long as the use pattern does not dramatically change and the potential for human exposure remains low. Furthermore, members of the Committee also believed that some of the registered uses for this chemical might fall under the jurisdiction of other sister agencies and thus are covered by provisions of the law administered by these agencies.

Based on the above, the Committee concluded that the chemical should be classified as a "Group D", not classifiable as for human carcinogenicity.

D. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity study (gavage) in rats (83-4, MRID No. 41097201) to be acceptable and the data evaluation record (HED Doc. 011532) to be adequate. The Committee recommended lowering the parental toxicity NOEL from 1.5 mg/kg/day to 0.5 mg/kg/day based on increased incidence of histopathologic skeletal muscle atrophy in the upper hind limb in both sexes. The reproductive NOEL/LOEL remain unchanged as 1.5 and 3.5 mg/kg/day. The Committee noted some discrepancies in the data evaluation record for this study. For example, effects mentioned on page 8 for the F1 males; this position was reversed and the effects were ruled out on page 11 of the data evaluation record. On page 11, the data evaluation record states that the effects were no longer evident in the F1 males. The Committee recommended that the data evaluation record be altered to reflect the Committee's position on the parental toxicity NOEL/LOEL and eliminate discrepancies mentioned above.

In the meeting of February 2, 1995, the Committee considered the dermal developmental toxicity study in rabbits (83-3b, MRID No. 40487201) to be unacceptable and recommended downgrading of the study, tentatively, from Core-minimum data to a Core-supplementary status for the lack of maternal toxicity. The Committee indicated

that the range-finding study should be submitted in order to upgrade the main study from Core-supplementary data to a Core-minimum status (if maternal toxicity was evident at the highest dose tested of 7.5 mg/kg/day). In the meeting of March 30, 1995, after reviewing the range finding study, the Committee concluded that the developmental toxicity study should remain as originally classifies as Core-minimum data. This conclusion was based on marginal maternal body weight gain decrements and a definitive body weight gain decrements observed at 5.0 and 7.5 mg/kg/day, respectively, in the range finding study.

Overall, the Committee concluded that reproductive toxicity occurred at highest dose level. No developmental toxicity was demonstrated at any dose level. Developmental neurotoxicity testing was not recommended since the use of this chemical is limited to non-food applications and because distinct neurotoxic effects such as hindlimb muscle atrophy in P0 and F1 adults (dosed in utero) at 1.5 mg/kg/day and the other effects observed in pups (possible developmental delays) at 3.5 mg/kg/day indicate that the effects occur in adults at lower dose levels.

E. Mutagenicity:

Several mutagenicity studies were available for review by the Committee including testing for gene mutation, testing for structural chromosomal aberration, and testing for other genotoxic effects.

The Committee considered the gene mutation assay in Chinese hamster ovary (CHO) cells (84-2a, MRID No. 40411501) to be acceptable and the data evaluation record to be adequate (HED Doc. No. 011532). The treatment did not induce any mutagenic response up to the highest dose tested of 0.08 µg/ml in the absence of a metabolic activation system and up to 11 µg/ml in the presence of a metabolic activation system.

The Committee considered the mouse micronucleus assay (84-2b, MRID No. 0343701) for structural chromosomal aberration to be acceptable and the data evaluation record (HED Doc. No. 011532) to be adequate. The test was negative up to the highest dose tested of 238 mg a.i./kg.

The Committee considered the unscheduled DNA synthesis in the primary rat hepatocytes (84-4, MRID No. 40387501) to be acceptable and the data evaluation record (HED Doc. No. 011532)to be adequate. The test was negative up to the highest dose tested of 300 ng/ml.

These tests satisfy the minimum testing requirements for mutagenicity under the pre-1991 Guideline for gene mutations, structural chromosomal aberrations, and other genotoxic effects. Based on the available evidence, there is no current concern for mutagenicity and no further testing is indicated.

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F. Reference Dose (RfD):

The Committee recommended that an RfD be established based on a chronic toxicity study in rats with a no-observable effect level of 0.5 mg/kg/day. Significant increase in the incidence of degeneration of the skeletal muscle of the hindlimbs in both sexes was observed at the next higher dose level of 1.5 mg/kg/day. An uncertainty factor (UF) of 100 was applied to account for both interspecies extrapolation and inraspecies variability. On this basis the RfD was calculated to be 0.005 mg/kg/day.

The use of the reproductive toxicity study with a no-observable effect level of 0.5 mg/kg/day for parental toxicity as a co-critical study to support the RfD assessment was also suggested. Systemic (neurotoxic) effects were observed at the next higher dose level of 1.5 mg/kg/day.

It should he noted that this chemical has not been reviewed by the FAO/WHO joint committee on pesticide residues (JMPR).

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G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB, RfD/Peer Review Committee Chairman), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), Rick Whiting, Dave Anderson, Kerry Dearfield, Susan Makris, Esther Rinde, Henry Spencer and William Sette. In attendance also was Arliene Aikins of RCAB/HED as an observer.

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

John Whalan

Roger Gardner

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke

CC: Stephanie Irene
Debra Edwards
Karl Baetcke
Roger Gardner
John Whalan
Karen Whitby
Albin Kocialski
Beth Doyle
Kerry Dearfield
RfD File
Caswell File

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H. Material Reviewed:

1. Husband, R. F. A. et al. (1991). 104-Week oral (gavage) combined carcinogenicity and toxicity study in the rat. MRID No. 42100901, HED Doc. No. 011532. Classification: Guideline data. This study satisfies data requirement 83-1a and -2a (or 83-5) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Husband, R. F. A. et al. (1991). 80-Week dermal carcinogenicity study in the mouse. MRID No. 42100801, HED Doc. No. 011532. Classification: Supplementary (as downgraded by the RfD Committee). This study, as presented, does not satisfy data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Johnson, D. E. (1989). One-year oral toxicity study in Cynomolgus monkeys. MRID No. 41178101, HED Doc. No. 011532. Classification: Core-minimum data. This study satisfy data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rodents.

4. Ridgeway, P. and Wood, C. M. (1989). Sodium Omadine: Rat two-generation reproduction toxicity study. MRID No. 41097201, HED Doc. No. 011532. 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. Keller, K. A. (1987). Dermal developmental toxicity study in New Zealand white rabbits with Sodium Omadine. MRID No. 40487201, HED Doc. No. 011532. Classification: Core-supplementary data. This study does not satisfies data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

6. Husband, R. F. A. et al. (1988). 90-Day oral (gavage) toxicity in the rat (neurotoxicity). MRID No. 40756901, HED Doc. No. 011532. Classification: Core-supplementary data. This study does not satisfy data requirement 82-7 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity in rats.

7. Taupin, P. J. Y. and Wood, C. M. (1988). 90-Day dermal toxicity study in the rat. MRID No. 40936201, HED Doc. No. 011532. Classification: Guideline data. This study satisfies data requirement 82-3 of Subpart F of the Pesticide Assessment Guideline for subchronic dermal toxicity testing in rats.

8. Ulrich, C. E. (1989). Thirteen week subchronic inhalation toxicity study on Sodium Omadine in rats. MRID No. 41178201, HED Doc. No. 011532. Classification: Core-minimum data. This

study satisfies data requirement 82-4 of Subpart F of the Pesticide Assessment Guideline for subchronic inhalation toxicity testing in rats.

9. Stankowski, L. F. (1987). Sodium Omadine: CHO/HGPRT mammalian cell forward gene mutation assay. MRID No. 40411501, HED Doc. No. 011532. Classification: Acceptable. This study satisfies data requirement 84-2a of Subpart F of the Pesticide Assessment Guideline for gene mutation assay.

10. Sorg, R. S. (1987). Sodium Omadine micronucleus test. MRID No. 40343701, HED Doc. No. 011532. Classification: Acceptable. This study satisfies data requirement 84-2b of Subpart F of the Pesticide Assessment Guideline for structural chromosomal aberrations assay.

11. Barfknecht, T. R. (1987). Sodium Omadine: Rat hepatocyte primary culture/DNA repair test. MRID No. 40387501, HED Doc. No. 011532. Classification: Acceptable. This study satisfies data requirement 84-4 of Subpart F of the Pesticide Assessment Guideline for other genotoxic effects.

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