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

014264

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

August 03, 2000

MEMORANDUM

SUBJECT: ***MSMA / DSMA*** - Report of the FQPA Safety Factor Committee

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
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TO: Diana Locke, Risk Assessor
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PC Code: 013803/013802

The FQPA Safety Factor Committee met on July 24, 2000 to evaluate the hazard and exposure data for Monosodium Methanearsonate (MSMA) and Disodium Methanearsonate (DSMA) The committee recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be **reduced to 3x** in assessing the risk posed by this chemical.

I. HAZARD ASSESSMENT

(*Memorandum:* A. Lowit et al. to B. Tarplee dated July 17, 2000)

A. Adequacy of the Toxicology Data Base

The toxicology data base for MSMA/DSMA is incomplete. Although prenatal developmental toxicity studies in rats and rabbits and a 2-generation reproduction study in rats with MSMA are available and considered to be acceptable, there are data gaps for acute and subchronic neurotoxicity studies in mice. These studies are required due to evidence of neurotoxicity observed in the 104-week oncogenicity study in mice (females of the 46 and 104 mg/kg/day groups exhibited increased incidences of hypersensitivity and tonic convulsions). Additional evidence of potential neurotoxicity observed in mice following oral exposure to MSMA is found in the literature (Refer to HED Doc. No. 014249 for further details regarding data requirements and neurotoxicity).

B. Determination of Susceptibility

There is no quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to *in utero* exposure in available developmental toxicity studies. There is also no quantitative or qualitative evidence of increased susceptibility of offspring observed in the two-generation reproduction study in rats. In the developmental toxicity studies and in the two-generation reproduction study, developmental / offspring effects were observed only at doses greater than those demonstrating maternal / parental toxicity.

C. Requirement of Developmental Neurotoxicity Study

The HIARC determined that the requirement of a developmental neurotoxicity study (DNT) with MSMA is "reserved" pending receipt of the acute and subchronic neurotoxicity studies in mice.

Additionally, the HED Metabolism Assessment Review Committee (MARC) concluded that the residues of toxicological concern associated with the use of MSMA/DSMA are MSMA *per se* and cacodylic acid expressed as As_2O_3. During its review and evaluation of cacodylic acid, the HIARC required that a DNT be conducted with cacodylic acid. This requirement was based on the observation of endocrine effects in the two-generation reproduction study and in subchronic and chronic studies in rats (Refer to HED Doc. No. 013422 for further details regarding data requirements for cacodylic acid). When available, the results of this study may indicate whether or not a DNT with MSMA is warranted.

II. EXPOSURE ASSESSMENTS

A. Dietary Food Exposure Considerations

(*Memorandum:* A. Lowit et al. to B. Tarplee dated July 17, 2000)

MSMA/DSMA are selective herbicides used on cotton, bearing citrus trees, non-bearing fruit, vines, and nut trees. Based on the metabolism studies conducted by the registrants for MSMA, as well as metabolism data for MSMA and DSMA from published sources, the HED Metabolism Assessment Review Committee (MARC) concluded that the residues of concern (i.e., that which is of toxicological concern and requires regulation) associated with the use of MSMA and DSMA are MSMA *per se* and cacodylic acid expressed as As_2O_3.

The half-life selected for MSMA modeling is approximately eight (8) months (240 days). Using the 240 day half-life for MSMA and the selected 103 day half-life for cacodylic acid, then approximately 220 days after an initial MSMA application cacodylic acid will read a maximum concentration of approximately 23% relative to the initial amount of MSMA applied. At the same time when cacodylic is at its maximum, MSMA would be at approximately 53% of its original amount. Based on the available data, it is unlikely that cacodylic acid would reach much more than 30-35% MSMA equivalents in soil.

Tolerances are established for residues of the herbicide methanearsonic acid (calculated as As_2O_3) from the application of the disodium and monosodium salts of methanearsonic acid in or on citrus fruit at 0.35 ppm, cottonseed at 0.7 ppm, and cottonseed hulls at 0.9 ppm (40 CFR §289). There are currently no established Codex MRLs.

The Agency has determined that no animal feeding studies are needed to determine secondary transfer of DSMA/MSMA residues of concern in milk, eggs, and edible tissues. Based on Total Radioactive Residue (TRR) values in tissues from ruminant and poultry metabolism studies on 1x feeding levels, there is no reasonable expectation of detectable MSMA residues in animal tissues, milk, and eggs resulting from use patterns being considered for reregistration. Residues in livestock can be classified under Category 3 of 40 CFR §180.6(a).

There are no monitoring data available for DSMA and MSMA (FDA Total Diet Study measured total As_2O_3). Crop field trial data are available for citrus and cotton:

> In one citrus study, 27 field trials were conducted to determine the magnitude of MSMA and cacodylic acid residues in/on grapefruit, lemons, limes, and oranges following side-by-side applications of representative DSMA and MSMA formulations according to the use patterns the registrants are supporting. Mature fruits were collected at 0-day PHI following the last of three applications of DSMA and MSMA formulations at 4.9 lb ai/A/application and 4.0 lb ai/A/application, respectively. All treated citrus fruits each bore residues of MSMA below the analytical method's limit of quantification (LOQ) of 0.05 ppm; all treated fruits also bore nondetectable (<0.05 ppm) residues of cacodylic acid except for three samples.

In one cotton study, 23 field trials were conducted to determine the magnitude of the residues of MSMA and cacodylic acid in/on ginned cottonseed following applications of a representative MSMA formulation according to two types of use patterns the registrants are supporting. The combined residues of MSMA and cacodylic acid in/on ginned cottonseed harvested 71-130 days were: (I) <0.10-<0.29 ppm following two directed spray applications at 2 lb ai/A/application; and (ii)<0.10-<0.20 ppm following a single topical application at 1 lb ai/A followed by a directed spray application at 2 lb ai/A. The raw agricultural commodity (RAC) that was analyzed in the submitted cotton field study was ginned cottonseed as opposed to undelinted cottonseed as per Table 1 (OPPTS 860.1000).

Percent crop treated (%CT) information is available. The Biological and Economic Analysis Division (BEAD) provided Quantitative Usage Analyses for DSMA and MSMA which indicate that the maximum %CT with DSMA is 0% for cotton (S. Smearman; 12/17/98) and the maximum %CT with MSMA is 0% for grapefruit, 1% for lemons, 1% for oranges, and 33% for cotton (S. Smearman; 12/28/98).

The HED Dietary Exposure Evaluation Model (DEEM) is used to assess the risk from acute and chronic dietary exposure to residues in food resulting from the use of MSMA. The degree of refinement of the DEEM analyses will be a Tier 2a. This consists of the use of the highest average field trial (HAFT) residues, processing factors, and zeros being incorporated for the percent of crop not treated.

B. Dietary Drinking Water Exposure Considerations
(*Memorandum:* A. Lowit et al. to B. Tarplee dated July 17, 2000)

MSMA, initially 100% at application time, will be partially transformed into cacodylic acid. Cacodylic acid, initially at zero concentration, will increase to a maximum over a period of months and then decline until the next seasonal application of MSMA. Studies indicate that the maximum amount of cacodylic acid produced by the metabolism of MSMA is chemically equivalent to 30 to 40% of the initial MSMA application. Therefore, depending on probabilistic and episodic rainfall/runoff events, a time-dependent, variable mixture of MSMA and cacodylic acid will be available for runoff.

The environmental fate database is sufficiently complete to characterize drinking water exposure for MSMA (equivalently DSMA). Environmental fate laboratory studies showed that MSMA was stable under all tested conditions, except microbial metabolism. That is, MSMA did not degrade under the influence of abiotic (sterile) chemical or photochemical processes in soil or water. Aerobic and anaerobic microbial processes are slow. The aerobic soil half-life selected for MSMA for modeling purposes is approximately eight months (240 days). Since MSMA is non-volatile, sorbs appreciably to soil, and is very soluble in water, volatilization of parent is not a route of dispersal. MSMA did not bioconcentrate in bluegill sunfish and has a minuscule octanol/water partitioning ratio, and therefore, there is little potential for bioconcentration. The principal identified metabolites are cacodylic acid (CA), arsenate, carbon dioxide, and volatile alkylarsines.

Monitoring sources include USGS (mostly ground water, but with some surface water), BASINS, STORET (surface water only), and published literature. Limited, but valuable, surface and groundwater data exist for speciated arsenic (MSMA, CA, arsenite and arsenate). In most cases, however, monitoring was for total arsenic (unspeciated) in areas not targeted for use. Thus, most monitoring data are generally not useful for estimating MSMA or CA exposure as such.

Drinking water Estimated Environmental Concentrations (EECs) for surface water will be based on a combination of monitoring and modeling. PRZM/EXAMS index reservoir modeling will be used to estimate exposure in surface water for comparison with monitoring data.

There will be no modeling for ground water since ground water exposure due to agricultural application is not expected based on soil sorption characteristics and supplemental field evidence. Although monitoring for MSMA and CA indicates a minor presence in ground water, this cannot be reasonably attributed to labeled agricultural use.

C. Non-Occupational (Residential) Exposure Considerations

(*Memorandum:* A. Lowit et al. to B. Tarplee dated July 17, 2000)

MSMA and DSMA are used in residential settings for selective weed control on turf (lawns and golf courses) and around ornamentals, buildings, fences, walls, flower beds, and gardens, brick and gravel walks, patios, curbs, gutters, sidewalks, and driveways. Children and infants would possibly be exposed when playing outdoors. MSMA and DSMA have no restrictions on the number of times it may be applied per year. For use on lawns, it would probably be used two or three times a year. For spot weed control, it could be used as often as necessary. The rate of application for homeowners are 5 lbs ai/acre for liquids and 4.14 lbs ai/acre granular for lawns and 6 lbs ai/acre liquids for weeds.

There is a turf residue dissipation study available for DSMA. This study can be used in estimating post-application exposure resulting from the use of MSMA in residential settings. The *Draft Standard Operating Procedures for Residential Exposure Assessments* will be used as the basis for all calculations. The assessment will include the recent changes made to the Residential SOPs with no deviations.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. Recommendation of the Factor

The Committee recommended that an FQPA safety factor is necessary for MSMA/DSMA since there are data gaps for acute and subchronic neurotoxicity studies in mice (the requirement of a developmental neurotoxicity study is "reserved").

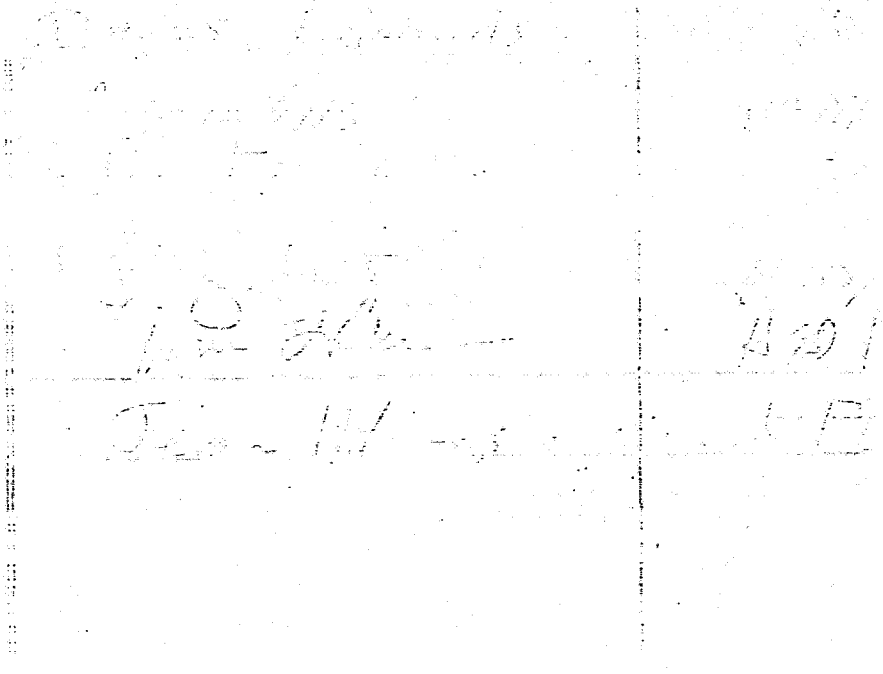
B. Rationale for Reducing the FQPA Safety Factor

The Committee concluded that the safety factor could be reduced to 3x for MSMA because:

1. There is no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure to rats and rabbits and/or following pre-/postnatal exposure to rats; and
2. The dietary (food and drinking water) and residential exposure assessments will not underestimate the potential exposures for infants, children, and/or women of childbearing age.

C. Application of the Safety Factor - Population Subgroups/Risk Assessment Scenarios

The FQPA safety factor for MSMA is applicable to **All Population Subgroups for Acute and Chronic Dietary Assessments and Residential Exposures Assessments of all Duration** since there are data gaps for acute and subchronic neurotoxicity studies in mice. Additionally, the requirement for a developmental neurotoxicity (DNT) study is "reserved" pending receipt of the neurotoxicity studies with MSMA (as well as the DNT with cacodylic acid). These studies will characterize the potential for neurotoxicity and may provide data that could be used in the toxicology endpoint selection for dietary and non-dietary risk assessments.



FQPA SAFETY FACTOR COMMITTEE MEETING

24JULY2000
MSMA/DSMA

Name	Division/Branch
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Debbie McCall	RD
Jess Rowlett	HED / RD
ALEX CLEM	EFED
Sherrie Kinard	HED / RRB2
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Renee Sandvig	"
Diana Locke	"
Dennis Edwards	AD
Susan Makris	HED / TOX1
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