ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR DISULFOTON

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CONTENTS

ADDENDUM FOR DISULFOTON

Supplement to the 1995 Toxicological Profile for Disulfoton

Background Statement

This addendum to the Toxicological Profile for Disulfoton supplements the profile that was released in 1995.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986, which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years." CERCLA further states that the Administrator will "establish and maintain an inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 1995.

Chapter numbers in this addendum coincide with those of the Toxicological Profile for Disulfoton (1995). This document should be used in conjunction with the profile. It does not replace it.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.2 Oral Exposure

2.2.2.4 Neurological Effects

In a study conducted by Jones et al. (1999), technical-grade disulfoton (DiSyston) was fed to male and female beagle dogs at nominal concentrations of 0, 0.5, 4, and 12 ppm for 1 year to characterize the potential general and neurovisual toxic effects of this compound at those doses. Plasma, erythrocyte, and corneal acetyl cholinesterase (AChE) activity was significantly depressed at 4 and 12 ppm in both sexes. Brain ChE was depressed at 4 and 12 ppm in females. Retinal cholinesterase was depressed at 4 ppm in females and at 12 ppm in males. Ciliary body AChE was depressed at 12 ppm in both sexes. Despite these adverse cholinergic effects, there were no adverse ophthalmologic findings, as measured by electroretinogram (ERG), tracking, refractivity, intraocular pressure, or pachymetry. There also were no clinical neurological findings related to disulfoton administration. The authors concluded that the toxicodynamics of disulfoton at the levels tested involved cholinergic effects on the plasma, erythron, brain, and certain ocular tissues, and that compensatory responses of the animals allowed for clinical neurologic and visual homeostasis to be maintained.

In a study conducted by Sheets et al. (1997), disulfoton and six other organophosphate insecticides were screened for neurotoxic potential in accordance with the protocols of the U.S. Environmental Protection Agency (EPA) Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Each organophosphate was administered through the diet for 13 weeks to separate groups of Fischer-344 rats at four dose levels,

including a vehicle control. The results showed that measures of AChE activity were consistently the most sensitive indices of disulfoton exposure and that such measures assisted in the interpretation of those findings. All treatment-related neurobehavioral findings were ascribed to cholinergic toxicity occurring only at dietary levels that produced more than 20% inhibition of plasma, red blood cells, and brain AChE. Treatment related effects included muscle fasciculations, tremors, increased reactivity and increased defecation. The lowest-observed-adverse- effect-level (LOAEL) for these clinical observations was 16 ppm; the no-observed-adverse-effect-level (NOAEL) was 1 ppm.

Acute and chronic exposure to disulfoton and other organophosphate pesticides may lead to persistent neurological and neurobehavioral deficits. A study conducted by Smulders et al. (2004) proposed that the etiology of these effects cannot be explained by AChE inhibition alone and suggests that other brain proteins are involved.

A study conducted by Matsuda et al. (2000) examined the effects of organophosphate exposure on mRNA expression levels of synaptic- and target tissue-specific proteins in rats. Rats were treated with a single dose of disulfoton and the authors measured the time course of changes in levels of mRNAs encoding AChE, nicotinic acetylcholine receptors (nAChR), β-enolase, and α-enolase in soleus muscles and sciatic nerves. The expression levels of mRNA encoding AChE in both tissues were significantly decreased, with a low point at 12 hours after chemical administration, and this down-regulation lasted for up to 30 days after administration. Similarly, the level of nAChR mRNA in the soleus muscle also decreased. These results indicate that administration of disulfoton and other organophosphates can decrease AChE and nAChR expression in the neuromuscular junction, and the results are suggestive of multiple mechanisms of down-regulation of both AChE and nAChR, some of which might involve alterations at the level of cellular transcription (mRNA synthesis).

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.3 Dermal Exposure

The Office of Pesticide Programs (OPP) of the U.S. EPA has developed a standard protocol for evaluating the dermal penetration of pesticides in the rat (Zendzian 2000). Dermal absorption data for disulfoton and over 160 other pesticide chemicals are presented in this study. From this standard protocol, it is possible to describe quantitatively with dose and time the entrance of disulfoton and penetration through the mammalian epidermis to the systemic circulation and its concentration in blood and in the body, and finally to its excretion in urine and feces. Rates of dermal absorption for disulfoton at a dose of 3.1 nanoMoles/cm^2 (nM/cm^2) ranged from 15.9 % of the administered dose at 1 hour to 42.0 % at 168 hours. Absorption at higher doses was lower, initially, but it approached the same maximum after 168 hours.

2.3.2 Distribution

In addition to studying dermal absorption, Zendzian (2000) evaluated systemic distribution of disulfoton. After 1 hour of dermal exposure to 3.1 nM/cm^2, the systemic distribution of disulfoton was 0.48 % of the administered dose in the blood and 4.84 % in the carcass, with these values reducing to 0.01 % and 0.09 %, respectively, at 168 hours.

2.3.5 Mechanisms of Action

Rats that were treated with a single dose of disulfoton exhibited a significant decrease in AChE mRNA levels in both soleus muscle and the sciatic nerve. Additionally, levels of nAChR mRNA in soleus muscle were reduced. These changes in expression of mRNA correlated with significant decreases in

levels of AChE and nAChR. These observations suggest that the down-regulation of both AChE and nAChR might involve alterations at the transcriptional (mRNA synthesis) level (Matsuda et al., 2000).

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.3 Sediment and Soil

The Salton Sea is the largest human-made lake in California and the largest continuous below-sea-level body of water in North America. It is officially designated by the State of California as an agricultural drainage reservoir. A study conducted by Sapozhnikova et al. (2004) determined disulfoton concentrations in sediments and fish tissue samples obtained from the Salton Sea. The concentration of disulfoton in sediment was below the level of detection (0.2 ng/g dry weight) in all sampling locations except one, where it was not detected in 2000 but it was measured in 2001 at 29.6 ng/g dry weight. Disulfoton was found in relatively high concentrations (up to 80.3 ng/g) in all organs of fish tested—i.e., Tilapia and Corvina. Mean concentrations were 20±17 ng/g in liver, 17±16 ng/g in gonads, 7±8 ng/g in

muscle, and 7±4 ng/g in gills. The range of concentrations for each organ in each fish generally spanned more than an order of magnitude. The disparity in sediment concentration at one location and the wide range of concentrations in fish organs indicates non-uniform environmental distribution but potentially high bioaccumulation when encountered by these fish.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

In a study conducted by Storm et al. (2000), toxicity and other relevant data for disulfoton and 29 other organophosphate pesticides were evaluated to determine inhalation occupational exposure limits (OELs) and to support development of a risk assessment strategy for organophosphates in general. Specifically, the study assessed the value of relative potency analysis and the predictability of inhalation OELs by acute toxicity measures and by repeated oral exposure at the No-Observable-Adverse-Effect Level. The OELs were derived by use of the endpoint of prevention of red blood cell AChE inhibition and by use of a weight-of-evidence risk assessment approach. When red blood cell AChE activity decreased to 70% (30% inhibition) of an individuals' baseline, it was concluded that the potential for overexposure to organophosphates exists and adverse effects may occur. It was advised that organophosphate exposures of workers experiencing this degree of red blood cell AChE inhibition be prevented until red blood cell AChE activity returned to baseline. Suggested OEL values for the entire group of organophosphates evaluated ranged from 0.002 to 2 mg/m^3. The suggested OEL for disulfoton specifically was 0.01 mg/m^3. The suggested OEL for disulfoton was less than the current threshold limit value (TLV) of 0.1 mg/m^3.

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

Toxicity and other relevant data were evaluated in a study conducted by Storm et al. (2000) to determine inhalation OELs. The suggested OEL value for disulfoton was 0.01 mg/m^3.

8. REFERENCES

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