ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR DINITROPHENOLS

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CONTENTS

ADDENDUM FOR DINITROPHENOLS

Supplement to the 1995 Toxicological Profile for Dinitrophenols

Background Statement

This addendum supplements the Toxicological Profile for Dinitrophenols that was released in 1995.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act of 1986, which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA).CERCLA mandates that the administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) prepare toxicological profiles on substances on the Priority List and that the profiles be revised "no less often than once every three years." CERCLA further states that the ATSDR administrator will "establish and maintain 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 the public and other federal, state, and local agencies a nonpeer reviewed supplement of the scientific data published in the open peer-reviewed literature since the profile's 1995 release.

Chapter numbers in this addendum coincide with the Toxicological Profile for Dinitrophenols (1995). This document does not replace the profile—rather, this document should be used in conjunction with the profile.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

Macnab and Fielden (1998) report on a farm child who became comatose and who was admitted to a hospital. Additional clinical signs and a search of the farm indicated that the child likely had been exposed to dinitrophenol (DNP) from an open container of the herbicide Dinoseb (2-*sec*-butyl-4, 6-dinitrophenol). No dose estimate was provided.

2.2.2. Oral Exposure

No updated data.

2.2.2.1 Death

Case studies are available of persons ingesting DNP in suicide attempts or to lose weight. Hsiao et al. (2005) reported the death of a17-year-old girl who died just 10 hours after she ingested between 12 and 15 diet pills (estimated DNP concentration of 192 mg/pill) in a suicide attempt. The calculated serum concentration of DNP was 315 µg/mL. Before death, the girl's symptoms included uncontrolled fever, agitation, combativeness, and mental status diminution. An autopsy revealed "profound" pulmonary edema, yellow staining of the skin and organs, and hepatic necrosis. McFee et al. (2004) reported the case of a 22-year-old man who, to lose weight, ingested an unknown quantity of 2, 4-DNP. He died 16 hours later. No blood concentrations were reported. Miranda et al. (2006) reported the deaths of two persons who died after they ingested unknown quantities of DNP. The blood concentrations of 2, 4-DNP at the time of admission for the two patients were 36.1 and 28 mg/L, respectively.

2.2.2.5 Reproductive Effects

Takahashi et al. (2003) reported results of a reproductive and developmental toxicity screening study in rats. These investigators administered 2, 4 -DNP by gavage at 30 mg/kg bw per day for 5 days. The 2, 4-DNP caused a slight increase in the incidence of tailless sperm. Takahashi et al. (2009) reported that no effects of 2, 4-DNP on estrous cyclicity, length of gestation, copulation, fertility and nursing indexes, and reproductive organs were observed in rats treated by gavage at 0, 3, 10, 30, or 80 mg/kg bw/day for 46 days.

2.2.2.6 Developmental Effects

Koizumi et al. (2001) reported that newborn rats were more susceptible to the toxic effects of 2, 4 -DNP than were older rats. In the newborn rat study of 2, 4-DNP, animals died at 30 mg/kg in the dose-finding study. In the main study, significant lowering of body and organ weights was observed at 20 mg/kg. In the 28-day young rat study, clear toxic signs followed by death occurred at 80 mg/kg, but no definitive toxicity was observed at 20 mg/kg. The study concluded that the toxic response in newborn rats is at most 4 times higher than that in young rats. Takahashi et al. (2003) reported developmental toxicity when investigators administered 2, 4-DNP by gavage at 30 mg/kg bw per day. A significant decrease in body weight gain and a significant increase in liver weight were found in males and females. The number of live pups on postnatal days (PNDs) 0 and 4, live birth index, and body weight of live male and female pups on PNDs 0 and 1 were significantly lowered at 30 mg/kg bw per day.

2.2.2.7 Genotoxic Effects

Hilliard et al. (1998) reported that 2, 4-DNP was an oxidative phosphorylation uncoupler that induced marked increases in chromosome aberrations with 26% and 38% cell aberrations. These were associated with considerable reductions in cell counts in Chinese hamster ovary cells.

2.3 TOXICOKINETICS

2.3.3 Metabolism

Politi et al (2007) used liquid chromatography-mass spectrometry to analyze biological fluids from a fatal poisoning case. They tentatively identified two possible conjugated DNP metabolites: 2-amino-4-nitrophenol glucuronide and 2, 4-dinitrophenol glucuronide.

2.3.5 Mechanisms of Action

Juthberg and Brismar (1997) studied the effects of 2, 4-DNP on metabolic inhibition on membrane potential and ion conductance. They concluded that 2, 4-DNP had specific effects on the plasmalemma in rat astrocytes; these effects may be due to an opening of calcium channels. Ravesloot and Rombouts (2000) suggest that 2, 4-DNP-induced toxicity may involve activation of ATP-sensitive K+ channels. Wu et al. (2000) reported increased ATP-sensitive K+ channel activity in pituitary GH3 cells treated with 2,4-DNP. Hudman et al. (2002) investigated the basis for DNP-induced increase in cytoplasmic calcium in rat cardiac myocytes. Their results indicated that the increase in cytoplasmic calcium occurs in two phases. The first phase appears to result from the release of mitochondrial calcium due to mitrochondrial depolarization. The second phase appears to be the result of a progressive release of calcium from the sarcoplasmic reticulum following depletion of intracellular ATP. Ribeiro et al. (2005) probed actomyosin interactions with 2, 4-DNP in an effort to understand chemo-mechanical coupling in muscle contraction.

Ribeiro et al. (2005) characterized DNP as an inhibitor of actin-myosin interactions. Han et al (2008a, 2008b) demonstrated that 2, 4-DNP is an uncoupler of oxidative posphorylation. Han et al. (2008b) indicated that 2,4-DNP, which induced reactive oxygen species (ROS) and reduced GSH content, inhibited the growth of human lung cancer cells via cell cycle arrest at G1 phase and apoptosis.

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

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

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.3 ENVIRONMENTAL FATE

No updated data.

5.2.2 Transformation and Degradation

No updated data.

5.3.2.2 Water

Takahashi et al. (1994) provided information on the environmental fate of DNPs. Five nitrophenols and two synthetic dyes were ozonated to evaluate 1) the biodegradability of reaction products from water quality parameters, and 2) the relationship between biodegradability and the behavior of the reaction products and the nitrogen forms. From the comparison of the biodegradability of the target compound,

Takahashi et al. confirmed that the variation of biodegradability was deeply associated with the behavior of the nitrogen forms.

Asman et al. (2005) monitored wet deposition of nitrophenols (including 2, 4-DNP) at two sites in Denmark and determined the contributions from regional sources. The concentrations of selected pesticides and of nitrophenols in rain were measured. Several of the compounds, including 2, 4-DNP could be detected but not quantified. The deposition of 2, 4-DNP was up to a factor of 40 higher than that of most of the pesticides tested. Asman et al. concluded that although these pesticides were not allowed in Denmark, they came in from other places and were transported at least 60–80 km.

6. ANALYTICAL METHODS

Hsiao et al. (2005) described a laboratory method that allowed post-mortem determination of the DNP concentration in serum using ultraviolet-visible spectrophotometry. The DNP concentration in the samples was determined from a plot of concentration vs. the absorbance generated from DNP standards.

7. REGULATIONS AND ADVISORIES

No updated data.

8. REFERENCES

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