ADDENDUM TO THE

TOXICOLOGICAL PROFILE FOR

2,3-Benzofuran

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ADDENDUM for 2,3-Benzofuran

Supplement to the 1992 Toxicological Profile for 2,3-Benzofuran

Background Statement

This addendum to the Toxicological Profile for 2,3-Benzofuran supplements the profile that was released in 1992.

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 1992.

Chapter numbers in this addendum coincide with the Toxicological Profile for 2,3-Benzofuran (1992). 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

2.2.1.7 GENOTOXIC EFFECTS

Robbiano et al. (2004) and Brambilla et al. (2004) have used *in-vitro* and *in-vivo* assays to identify tissue- and species-specific carcinogens that the standard tests examining genotoxicity are incapable of identifying. The investigators used this approach to identify chemicals that were genotoxic to specific organs (e.g., kidney) of rodents and human cell cultures. The investigators examined benzofuran and other chemicals to determine whether the battery of *in-vitro* and *in-vivo* assays of these chemicals consistently produced a positive correlation with the induction of rat kidney tumors. In addition, they investigated whether a quantitative similarity existed in the observed genotoxic effect between primary cultures of human kidney cells and rat kidney cells. Benzofuran has been shown to increase the incidence of renal-cell adenocarcinomas in female rats but not in male rats, and has been labeled a possible human carcinogen (group 2B) based on this finding. Using the Comet assay, benzofuran was investigated *in-vitro* and *in-vivo* to determine its ability to induce DNA fragmentation and to determine if a rise in the frequency of micronuclei in kidney cells occurred. Primary cultures of kidney cells from both rats and humans were examined using the *in-vitro* assays. DNA fragmentation and micronuclei formation were investigated *in-vivo* for the kidneys of rats administered the chemical orally. *In-vitro* studies (Comet assay) examined cytotoxicity and DNA fragmentation immediately after a 20-hour exposure to benzofuran. Concentrations of benzofuran were based on a preliminary cytotoxicity assay with the highest concentration producing a cell viability of <30%. This was to prevent toxicity-induced, unspecific DNA damage. The micronucleus assay was implemented by incubating rat and human kidney cells in serial concentrations of benzofuran for 48 hours. The frequency of micronucleated cells was then ascertained. *In-vivo* studies examined DNA fragmentation and micronuclei in euthanized Sprague-Dawley rats that had been given a single oral dose (1/2 LD_{50}) of benzofuran and other test chemicals. The study results demonstrated that benzofuran induced a dose-dependent rise in the frequency of DNA lesions in kidney cells of

female rats exposed to benzofuran at concentrations ranging from 0.125 millimolar (mM) to 0.50 mM. The study also showed that benzofuran as a carcinogen in female rat kidneys produced genotoxic effects that resembled effects seen in primary cultures of human kidney cells. A dose-dependent DNA fragmentation was also seen in human kidney cells. These results showed that short-term genotoxicity assays may identify kidney carcinogens using kidney cells, and that benzofuran and other test chemicals affected primary cultures of human kidney cells and rat kidney cells similarly.

2.3 TOXICOKINETICS

2.3.3 Metabolism

Connelly et al. (2002) used high performance liquid chromatography-nuclear magnetic resonance (HPLC-NMR), high performance liquid chromatography-nuclear magnetic resonance-mass spectrometry (HPLC-NMR-MS), and hydrogen nuclear magnetic resonance (^{1}H NMR) to structurally characterize the urinary metabolites of 2,3-benzofuran (BF) in Sprague-Dawley rats following intraperitoneal injection. The lowest documented dose of BF that had been reported to cause histopathological changes in the rodent liver was 150 milligram per kilogram (mg/kg (Connelly 1983). Groups of five rats received either BF at 150 mg/kg or a dose of saline. No other doses were administered. Background urine specimens were collected before exposure, and as much as 168 hours after exposure. ^{1}H NMR spectroscopic examination of urine collected at 0–8 hours and 8–24 hours identified peaks considered to be BF metabolites (metabolite A and metabolite B). HPLC-NMR was used to analyze the metabolite A again. MS and NMR identified the structure of metabolite A as 2-hydroxyphenylacetic acid. ^{1}H NMR and MS identified the structure of metabolite B as 2-(2-hydroxyethyl) phenol conjugated with one sulfate group. Forty-four percent of the original administered dose of BF was eliminated as the two identified metabolites during the first 24 hours after initial administration. Of that amount, 24% of the BF dose was excreted as 2-hydroxyphenylacetic acid and 19.6% was excreted as 2-(2-hydroxyethyl) phenyl hydrogen sulfate. The proposed metabolism of BF involves cleavage of the furan ring to

2-hydroxyphenylacetic acid, or reduction and sulfation to form 2-(2-hydroxyethyl) phenyl hydrogen sulfate.

2.3.5 Mechanisms of Action

Russom et al. (1997) investigated the relationship between acute toxic action modes and quantitative structure activity relationships (QSAR) in fathead minnows. Using a database of 600 chemicals (Brooke et al. 1984), data relating substructural fragments of chemicals to modes of toxic action were created, and the chemicals were categorized according to one of eight modes of action: narcosis (I, II, III), uncoupling oxidative phosphorylation, respiratory inhibition, electrophilic/proelectrophile reactivity, acetylcholinesterase inhibition, or central nervous system-seizure responses. As a reactive toxicant, 2,3-benzofuran was categorized as electrophilic/proelectrophilic.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

- Identification Number: UN Shipping (Hazard Class)–3 (International Chemical Safety Cards 2002)

3.2 CHEMICAL AND PHYSICAL PROPERTIES

- Vapor pressure, kPa @25°C: 0.06 (International Chemical Safety Cards 2002)
- Flash point: 56°C (International Chemical Safety Cards 2002)
- Explosive limits: >56°C explosive vapor/air mixture may be formed (International Chemical Safety Cards 2002)

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

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

In 2001, EPA created a list of compounds emitted from on-road and non-road mobile sources which they called a Master List of Compounds Emitted by Mobile Sources. Compounds selected for this master list were compiled from references dealing with fuel from on-road and non-road mobile sources. Since the publication of the original profile, there has been no new information available in the literature to indicate that new sources of 2,3-benzofuran releases occurred. However, in 2006, EPA added the chemical to the Master List of Compounds emitted by mobile sources (EPA 2006).

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

Based on cancer incidence in National Toxicology Program rodent studies (see discussion in the ATSDR 1992 *Toxicological Profile for 2,3-Benzofuran*), the International Agency for Research on Cancer (IARC) classified 2,3-benzofuran as Group B; possibly carcinogenic to humans (IARC 1995)

8. REFERENCES

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