Addendum to the Toxicological Profile for 2-Hexanone

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ADDENDUM FOR 2-Hexanone
Supplement to the 1992 Toxicological Profile for 2-Hexanone

Background Statement

This addendum for 2-Hexanone supplements the Toxicological Profile for 2-Hexanone 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 Priority List and that the profiles be revised "no less often than once every three years". CERCLA further states that the 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, to the public, other federal, state, and local agencies a non-peer reviewed supplement of the scientific data that was 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-Hexanone (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 Inhalation Exposure

Many animal studies have been located regarding inhalation exposure to 2-hexanone, but some of these studies did not provide information on the purity of 2-hexanone. The usefulness of the data is limited because of confounding variables, which provided uncertainty regarding whether exposure was to pure 2-hexanone or to an uncertain extent of 2-hexanone in a chemical mixture.

Hepatic Effects. In rats, inhalation exposure to 2-hexanone has been shown to induce certain isomers of cytochrome P-450 and increase in liver weight. (Nakajima et al. 1991).

***Gastrointestinal Effects*.** Potentiated cholestasis (arrest in bile flow) was observed in rats that inhaled 2-hexanone and methyl isobutyl ketone for 3 days, 4 hours/day (levels not reported). It was determined that 2-hexnone was more potent in this effect than methyl isobutyl ketone (Duguay and Plaa, 1997). These investigators suggested that, although the mechanism of ketone-induced cholestasis is not known, the increased bile canalicular membrane cholesterol content and enhanced accumulation of newly synthesized cholesterol may be involved in the increased effects of ketones on cholestasis (Duguay and Plaa, 1997).

2.2.1.4 Neurological Effects

Since the Toxicological Profile for 2-hexanone was issued in 1992, some new animal studies have emerged concerning the neurological effects from exposure to 2-hexanaone via inhalation. Elke et al., (1995) observed (in rats) that axonal atrophy is a potentially significant pathogenic event occurring in central and peripheral distal axonopathy.

2.2.1.8 Cancer

In order to assess the toxic and carcinogenic effects of 2-hexanone, F-344/N rats and B6C3F1 mice were exposed via inhalation to 2-hexanone at 0, 450, 900, or 1,800 ppm for 6 hours/day for 5 days/week for 2 years. These investigators observed a decrease in body weight of male rats that were exposed to 900 ppm and in female mice that were exposed to 1,800 ppm. The target organs in these animals appeared to be the kidney for rats and the liver for mice (Stout et al., 2008). There was a higher incidence of renal tubule hyperplasia as well as increases in adenoma and carcinoma at 1,800 ppm (Stout et al., 2008). The incidence of chronic severe progressive nephropathy may have resulted from the increases in the other parameters, such as renal tubule hyperplasia. Furthermore, these results indicate that adrenal medulla hyperplasia was increased at 1,800 ppm of exposure to 2-hexanone and that there was a positive trend for increases in benign and malignant tumors (Stout et al., 2008).

2.3 TOXICOKINETICS

2.3.3 Metabolism

By using n-hexane as a prototype substrate, it has been demonstrated in rats that skeletal muscle microsomes have low levels of extra hepatic xenobiotic metabolism (Crosbie et al., 1997). Metabolism of n-hexane to 1, 2, and 3-hexanol, and 2-hexanone has been demonstrated in cultured rat myoblasts (Crosbie et al., 1997).

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

When it is necessary to investigate biological markers of occupational exposure to solvents, it appears plausible to collect urine samples rather than blood samples, because urine collection is considered a non-invasive sampling method (Kawai et al., 2003). Furthermore, urine and blood measurements of 2-hexanone and its metabolites may not reflect an adequate indication of exposure to this substance, since 2-hexanone and its metabolites may also result from exposure to n-hexane. Therefore, it has been suggested that it is better to assay for the un-metabolized solvent or the parent compound as an exposure marker, because its urinary excretion is primarily a function of its physico-chemical properties and will not be influenced very much by the differences in the metabolic or bio-transformation capacity of an individual (Kawai et al., 2003). Rats that received i.p. injections of 2-hexanone for 4 days manifested biomarkers of effects that included increased liver weights and increased levels of certain isomers of cytochrome P-450 in comparison to their corresponding controls (Nakajima et al., 1991).

3. CHEMCIAL AND PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

No updated data.

5.3 ENVIRONMENTAL FATE

2-Hexanone was produced and used as an industrial solvent for many materials, including lacquers, resins, oils, nitrocellulose, acrylates, and vinyl and alkyl coatings. However, the chemical is no longer produced in the United States, and its uses are restricted. The environmental half life of the vapor phase of 2-hexanone is about 2 days; one reason is its reaction with photo-chemically produced hydroxyl radicals (HSDB, 2009).

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

Since 1992, the Occupational Safety and Health Administration (OSHA) has set a new Time Weighted Average (TVA) exposure limit of 100 ppm (i.e., 100 parts of 2-hexanone in 1 million parts of air) as an average level for a 40 hr work week. OSHA has set a Short Term Exposure Limit (STEL) of 10 ppm in which the air is measured over a 15 minute period unless noted otherwise (NIOSH Pocket Guide, 2009).

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