ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR HEXACHLOROBUTADIENE

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ADDENDUM FOR HEXACHLOROBUTADIENE
Supplement to the 1994 Toxicological Profile for Hexachlorobutadiene

Background Statement

This addendum to the Toxicological Profile for Hexachlorobutadiene supplements the profile that was released in 1994.

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 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 1994.

Chapter numbers in this addendum coincide with the Toxicological Profile for Hexachlorobutadiene (1994). 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

2.2.1.2 Systemic Effects

Renal Effects. Staples et al. (2003) conducted a longitudinal study investigating changes in renal glomerular and tubular function in 70 residents of houses found to have hexachlorobutadiene concentrations >0.6 ppb in air; all subjects had vacated their homes within a period of 2 months prior to the beginning of the testing. Site-specific urinary markers of early tubular and glomerular effects (albumin, transferring, retinol binding protein, N-acetyl-β-glucosaminidase, γ-glutamyltransferase, leucine aminopeptidase, α-glutathione-S-transferase, π-glutathione-S-transferase) were used to assess renal function. Increased prevalences of abnormal levels of α-glutathione-S-transferase (22%), γ-glutamyltransferase (22%), leucine aminopeptidase (19%), and π-glutathione-S-transferase (22%) were found when the urinary biomarker values for 47 of the participants (children under 16 years and subjects older than 65 years were excluded) were compared to values in "healthy workers" with no history of exposure to nephrotoxicants. When these 47 participants were retested 10 months after leaving their homes, significant decreases in biomarkers of proximal and distal tubular damage were observed; the prevalence of abnormal γ-glutamyltransferase was the only biomarker with prevalence >10%.

2.2.2 Oral Exposure

2.2.2.2 Systemic Effects

Renal Effects. Four male and four female Wistar rats were administered a single gavage dose of 200/kg ^{14}C-hexachlorobutadiene in corn oil; the animals were sacrificed 48 hours after exposure and the kidneys and liver were examined (Birner et al. 1995) Extensive epithelial necrosis of the proximal tubules were observed in both male and female rats; however, males showed an increased extent of necrosis to the pars recta of the proximal tubules compared to females.

Hepatic Effects. The livers of female rats showed no liver histology changes, but male rats exhibited slight centrilobular liver toxicity (Birner et al. 1995). The study also described a new pathway of

hexachlorobutadiene biotransformation in male rats that may have contributed to sex differences in hexachlorobutadiene nephrotoxicity (see Section 2.3.3).

2.3 TOXICOKINETICS

2.3.3 Metabolism

Metabolism rates of hexachlorobutadiene were examined *in vitro* in rat and human tissues at several metabolic steps (Green et al. 2003). The rate of conjugation (VMAX) of hexachlorobutadiene in liver microsomal fraction in rat cells was found to be 5 times higher than in human liver cell, and the affinity constant (KM) was found to be about 1.3 times higher in rat cells. The metabolic rate of hexachlorobutadiene-CYS by renal β-lyases was not detected in human kidney cytosol, and is at least 23 times lower than the rate in rat kidney cytosol. In rats, metabolism by β-lyases in renal mitochondrial fractions was 4 times greater than in the cytosol. Human mitochondrial cells also showed some metabolism by β-lyases, but at lower rates than rat cells, while affinity constants for mitochondrial enzymes were statistically similar. Metabolism of hexachlorobutadiene-CYS to N-acetylcysteine conjugate was active in both rat and human kidney fractions, showing higher VMAX rates than metabolism by β-lyases. Metabolism for hexachlorobutadiene-NAC by acylases was detected in rats, but not in human kidney fractions. Using a physiologically based toxicokinetic model, metabolism by the β-lyase pathway for inhalation exposure was predicted to be 1 order of magnitude higher in rats than in humans.

Several studies investigated gender-related differences in metabolism of hexachlorobutadiene. In male and female Wistar rats administered 200 mg/kg ^{14}C-hexachlorobutadiene as a single gavage dose, no significant differences between male and female rats in the disposition and excretion rates of ^{14}C-hexachlorobutadiene-derived radioactivity were found (Birner et al. 1995). There were, however, differences in the radioactive profiles of the urine between male and female rats. In the females, the major radioactive peak was associated with the metabolite, *N*-acetyl-S-1, 2, 3, 4, 4-pentachlorobutadienyl)-L-cysteine (N-ac-PCBC); small amounts of S-(1, 2, 3, 4, 4-pentachlorobutadienyl)-L-cysteine were also detected. In contrast, the major radioactive peaks in male rats were associated with the metabolite N-ac-PBC sulfoxide and unchanged ^{14}C-hexachlorobutadiene (Birner et al. 1995). The formation of N-ac-PCBC sulfoxide from N-ac-PCBC was catalyzed *in vitro* in male rat liver microsomes, but not in female liver microsomes. In a study by Pahler et al. (1995), unmetabolized hexachlorobutadiene was detected in the urine of male Sprague-Dawley rats receiving a single gavage administration of 200 mg/kg ^{14}C-hexachlorobutadiene. However, it was not detected in the

urine of female rats or in male or female NCI Black-Reiter rats (an α_{2u}-globulin-deficient strain). The measured radioactivity was found to be associated with the α_{2u}-globulin fractions of urine and renal cytosol of the male Sprague-Dawley rats.

2.2.4 OTHER EXPOSURE ROUTES

Renal Effects. Wistar albino rats (number of animals not specified) were administered intraperitoneal injections of 0 (corn oil) or 25 mg/kg hexachlorobutadiene for 2, 3, 4, or 7 days (Boroushaki 2003). Necrosis to the straight portion of the proximal tubules was noted in animals treated for 2 and 3 days. Regeneration of the renal proximal tubules was seen in animals treated for 4 days, and the kidneys of animals treated for 7 days appeared normal, suggesting the development of resistance to hexachlorobutadiene toxicity in the kidneys. Further testing of exposure to 25 and 100 mg/kg hexachlorobutadiene for 18 and 25 days showed continued resistance to kidney damage by hexachlorobutadiene, with the 18- and 25-day exposed animals showing significantly less kidney damage than the 2-day exposed animals . In animals re-exposed to the high dose of hexachlorobutadiene, data showed that the susceptibility to hexachlorobutadiene was starting to return.

Cristofori et al (2007) investigated male Wistar rats treated with segment-specific nephrotoxicants. In the study, male rats were treated with a single intraperitoneal injection of hexachlorobutadiene (100 mg/kg b.w.) at five weeks or 12 weeks of age. Twenty-four and forty eight hours after treatment, the rats were sacrificed and the kidneys were drawn for histopathological and biochemical evaluations. Histopathological findings showed that hexachlorobutadiene caused diffuse necrosis of the S3 segment of proximal tubules in the outer stripe of outer medulla.

Zanetti et al (2009) studied the age-dependent response of the kidney to hexachlorobutadiene. Rats were treated at different ages with a single intraperitoneal injection of 1000 mg/kg hexachlorobutadiene in corn oil. Treatment induced tubular necrosis of the S3 segment of the proximal tubule associated with changes of toxicological markers unrelated to age. The *in vitro* metabolic studies by Green et al. (2003) in rat and human tissue, previously discussed in the Metabolism Section (2.3.3), would suggest that humans may be less susceptible to butadiene-induced renal toxicity than rats.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

2.5.2 Biomarkers Used to Characterize Effects Caused by Hexachlorobutadiene

In a study examining the use of gene expression patterns as biomarkers for proximal tubular toxicity in Sprague-Dawley rats resulting from exposure to hexachlorobutadiene as well as a number of other site-specific (i.e.; proximal tubules) nephrotoxic compounds, several transporters (Slc21a2, Slc15, Slc34a2), Kim1, IGFbp-1, osteopontin, α-fibrogen, and Gstα were shown to be potential biomarkers showing a time- and dose-dependent response associated with proximal tubular toxicity (Thukral et al. 2005).

Another study investigating possible biomarkers in relation to segment-specific renal toxicants showed that glutathione synthetase activity is indicative of injury to the S_3 segment of the proximal tubules (Cristofori et al. 2007). Hexachlorobutadiene in corn oil was administered to Wistar rats by a single intraperitoneal injection at a dose of 0 or 100 mg/kg. Necrosis of the S_3 segment of the proximal tubules in the outer stripe of the outer medulla (determined by histopathological examination) resulting from hexachlorobutadiene exposure was associated with decreased glutathione synthetase activity.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Bouthillier et al. (1996) assessed the role of glutathione conjugation as the mechanism by which anethol dithiolthione (ADT) protects against renal toxicity resulting from hexachlorobutadiene exposure. The study showed that ADT does not protect against hexachlorobutadiene-induced nephrotoxicity through glutathione conjugation in the liver, or by the modulation of non-protein sulfhydryl (NPSH) content or β-lyase activity. It is suggested that the ADT protection of hexachlorobutadiene-induced nephrotoxicity takes place in the kidney downstream of the metabolism of hexachlorobutadiene to the nephrotoxic cysteine conjugate, pentachlorobutadienyl-L-cysteine (PCBC).

Bouroshaki et al. (2010) studied the effect of pomegranate seed oil on hexachlorobutadiene-induced nephrotoxicity in adult male rats. Pomegranate seed oil pretreatment resulted in a significant and dose-dependent decrease in serum creatinine and urea levels. Pomegranate seed oil also significantly reversed the Hexachlorobutadiene-induced depletion of total thiol content and thiobarbituric acid (TBARS) in kidney (TBARS, as an index of lipid peroxidation). Results of the study showed that pomegranate seed

oil attenuated hexachlorobutadiene-induced nephrotoxicity; the mechanism of this effect was not identified.
Hexachlorobutadiene was found to be negative for estrogenic activity in a yeast two-hybrid assay screening system based on the ligand-dependent interaction of estrogen receptor, ERα, and its co activator, TIF2 (Nishihara 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

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The desorption of hexachlorobutadiene from field samples of contaminated soil to water was shown to occur in two stages, a loosely bound stage and a tightly bound stage, exhibiting a hysteresis effect on desorption. The initial partitioning from desorption of loosely bound hexachlorobutadiene in soil is quicker than the more tightly bound hexachlorobutadiene desorption characterized as a long-term resistant phase (Chen et al. 1999; Kommalapati et al. 2002).

Bioaccumulation factors based on freely dissolved lipid-normalized concentrations in water for hexachlorobutadiene range from 3.83 to 5.76 in various aquatic species including *Callinectes sapidus*, *Fundulus heteroclitus*, *Micropoganias undulates*, and *Brevoortia patronus* (Burkhard et al. 1997).

The mean concentration of hexachlorobutadiene found in fish in a contaminated swamp in the lower Mississippi River in Baton Rouge, Louisiana was more than 300 times greater than the mean sediment concentrations suggesting high bioaccumulation (Bart et al. 1998).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Abdelghani et al. (1995) conducted field and laboratory studies to determine the levels of hexachlorobutadiene in various samples collected from a swamp area in Louisiana. Hexachlorobutadiene levels ranged from less than 0.01 to 0.48 ppb in water samples, and from less than 0.05 to 0.40 ppb in sediment samples.

5.4.4 Other Environmental Media

In a survey of chemical residues in bottom feeding and game fish in 400 sites in the United States, hexachlorobutadiene was found at a mean concentration of 0.6 ng/g (standard deviation: 8.7) in 3% of the sites; the highest concentration was found in the Calcasieu River watershed in Louisiana in sea catfish at a concentration of 164 ng/g (Kuehl et al. 1994).

Macgregor et al. (2010) investigated concentrations of persistent organic pollutants (POPS) including hexachlorobutadiene in eels from 30 sites across Scotland. While several of the other POPS were detected in all samples, hexachlorobutadiene was detected in only one sample. Eels were used as an ideal biomonitor because of their high lipid content.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Fat tissue samples from 50 children living in farm areas in the Murcia region of Spain were found to have a mean concentrations of hexachlorobutadiene of 0.70 ug/g (from 13 positive samples) ranging from 0.23 to 2.43 μg/g (Olea et al. 1999).

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Hexachlorobutadiene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	0.0006 mg/L	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)[b]	0.02 ppm	ACGIH 2008
	TLV-basis (critical effect)	Kidney damage	
NIOSH	REL (10-hour TWA)[c]	0.02 ppm (0.24 mg/m^3)	NIOSH 2005
	IDLH	No	
	Potential occupational carcinogens	Yes	
	Target organs	Eyes, skin, respiratory system, kidneys	
OSHA	PEL (8-hour TWA) for general industry	No[d]	OSHA 2009
b. Water			
EPA	Drinking water standards and health advisories		EPA 2006
	1-day health advisory for a 10-kg child	0.3 mg/L	
	10-day health advisory for a 10-kg child	0.3 mg/L	
	DWEL	0.01 mg/L	
	Lifetime	No	
	10^{-4} Cancer risk	0.09 mg/L	
	National primary drinking water standards	No	EPA 2009
NATIONAL *(cont.)*			
c. Other			
ACGIH	Carcinogenicity classification	A3[e]	ACGIH 2008
	Biological exposure indices (end of shift at end of workweek)	No	
EPA	Carcinogenicity classification	C[f]	IRIS 2009
	RfC	No	
	RfD	Withdrawn	

Table 7-1. Regulations and Guidelines Applicable to Hexachlorobutadiene

Agency	Description	Information	Reference
NTP	Carcinogenicity classification	No	NTP 2005

[a]Group 3: not classifiable as to carcinogenicity to humans.
[b]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids.
[c]Skin designation
[d]On January 19, 1989, OSHA published its final rule on Air Contaminants, which amended 29 CFR 1910.1000 by lowering 212 of OSHA's existing PELs for toxic substances and setting PELs for 164 toxic substances that had been previously unregulated. However, on July 7, 1992, the Eleventh Circuit Court of Appeals issued a decision in American Federation of Labor-Congress of Industrial Organization (AFL-CIO) v. OSHA that vacated these revised standards.
[e]A3: confirmed animal carcinogen with unknown relevance to humans.
[f]Classification C: possible human carcinogen; based on observation of renal neoplasms in male and female rats in one study.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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