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ADDENDUM TO THE

TOXICOLOGICAL PROFILE FOR

2-BUTANONE

Agency for Toxic Substances and Disease Registry

Division of Toxicology and Environmental Medicine

Atlanta, GA 30333

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ADDENDUM FOR 2-BUTANONE

Supplement to the 1992 Toxicological Profile for 2-Butanone

Background Statement

This addendum to the Toxicological Profile for 2-Butanone supplements the profile 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 ATSDR's Administrator 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 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-Butanone (1992). This document should be used in conjunction with the profile; it does not replace the profile.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.2 Systemic Effects

Respiratory Effects. In a cross-over design study, 19 men were exposed to either 0 or 200 ppm of 2-butanone for 4 hours, then 1 week later exposed to the other dose (Muttray et al. 2002). Subjects, who were not blinded because of the odorous nature of the substance, were asked to rate the severity of several symptoms before, then at 2 hours and 4 hours of exposure, with 0 being no effect and 5 being a severe effect, via the Swedish performance evaluation system (SPES). Although the median score for all symptoms was 0, a few of the subjects did report a significant increase in the severity of throat irritation after 4 hours of exposure. Significant increases in nasal mucociliary transport time were observed after exposure to 200ppm of 2-butanone. Non-significant increases in interleukin (IL)-1β and IL-8 levels were measured in nasal secretions; no alterations in IL-6 levels or tumor necrosis factor-α (TNFα) were found. These findings suggest subclinical rhinitis.

Impaired lung function was reported in four subgroups of workers (leather, rubber, or plastic workers, and tailors used as the control group) exposed to 2-butanone, leather dust, and solvents in a shoe production facility (Oleru and Onyekwere 1992). No information on exposure concentrations was provided. A significant decrease in 1-second forced expiratory volume (FEV_1) was observed; forced vital capacity (FVC) was not significantly affected. All groups showed deficits in pulmonary function, with the ratio of FEV_1 to FVC significantly correlated with age and duration of exposure. Work stations were not isolated

and the leather workers may have been exposed to other substances, including rubber, silica, zinc oxide, sulfur, carbon black, and polyvinyl chloride, used in the facility.

An increased prevalence of upper respiratory tract irritation (statistical significance not reported) was observed in a group of 41 workers exposed to 2-butanone at a cable factory, compared with a control group of 63 workers (Mitran et al. 1997). The exposure-level range throughout an 8-hour shift was 149–342 mg/m^3 (50.8–117 ppm), which is entirely within accepted occupational exposure limits (OSHA 2009). Although the EPA IRIS on acetone (EPA 2002) and a letter to the editor (Graham 2000) cite concerns with the 1997 Mitran study, these concerns pertain particularly to the appropriateness of using that study to establish a Reference Concentration (RfC) or modify health guidance values.

Gastrointestinal Effects. A higher prevalence of gastrointestinal symptoms (including loss of appetite, hyperacidity, bad taste, and abdominal pains) was observed in 41 workers exposed to 149–342 mg/m^3 (50.8–117 ppm) of 2-butanone, compared with 63 control workers (Mitran et al. 1997); statistical analysis of the prevalence data was not conducted.

Musculoskeletal Effects. Increased pain in the bones, joints, and vertebral column and diffuse muscular pain were reported by a majority of 41 cable factory workers exposed to 2-butanone, compared with 63 controls (Mitran et al. 1997). The exposure-level range throughout an 8-hour shift was 149–342 mg/m^3 (50.8–117 ppm), which is entirely within accepted occupational exposure limits (OSHA 2009). Although the EPA IRIS on acetone (EPA 2002) and a letter to the editor (Graham 2000) cite concerns with the 1997 Mitran study, these concerns

pertain particularly to the appropriateness of using that study to establish an RfC or modify health guidance values.

Dermal/Ocular Effects. A group of 41 workers exposed to 2-butanone reported a higher incidence of ocular symptoms and skin irritation, compared with a control group of 63 workers (Mitran et al. 1997). The exposure-level range throughout an 8-hour shift was149–342 mg/m^3 (50.8–117 ppm), which is entirely within accepted occupational exposure limits (OSHA 2009). Although the EPA IRIS on acetone (EPA 2002) and a letter to the editor (Graham 2000) cite concerns with the 1997 Mitran study, these concerns pertain particularly to the appropriateness of using that study to establish an RfC or modify health guidance values.

2.2.1.4 Neurological Effects

Two studies have examined the neurotoxicity of 2-butanone following acute-duration exposure to humans. In one study, 12 males and 13 females were exposed to 200 ppm 2-butanone for 4 hours. Psychomotor and sensorimotor tests were conducted before, during, and after exposure (Dick et al. 1992). In the Profile of Mood Scales (POMS) test of subjective symptoms, significantly higher vigor scores were found in the post-exposure period. In the neurobehavioral tests, a negative linear trend with 2-butanone blood concentrations and movement time in the choice reaction test was found in men, and a positive linear relationship between 2-butanone blood concentration and percent incorrect responses in the dual task test was found in women.

In an acute-duration study designed to assess potential respiratory effects in 19 men after a 4-hour exposure to both 0 and 200 ppm 2-butanone, done on different days, significant increases in the severity of headache and nausea were reported by the subjects 2 hours after exposure began to the 200 ppm exposure, compared with pre-exposure ratings (Muttray et al. 2002).

Neurological effects were also discussed in two case reports of workers chronically exposed to 2-butanone. One report discusses effects observed in a worker testing the properties of building materials for 7 months (Callender 1995). The worker primarily was exposed to 2-butanone daily, the fumes generated from burning fiberglass material, and occasionally to peroxides and acetone. Exposure concentrations were not reported. The worker self-reported to the physician a number of neurological symptoms, including severe chronic headache, dizziness, loss of balance, memory loss, fatigue, tremors, muscle twitches, visual disturbances, throat irritation, and tachycardia. Neurobehavioral tests revealed mild-to-moderate impairment of attention, psychomotor speed, short-term memory, and the ability to shift cognitive sets as processing demands increased, as well as significant mood disruption in the form of depression. EEG and evoked potentials tests showed abnormalities that were consistent with behavioral effects. Additionally, motor and sensory polyneuropathy was found in nerve conduction velocity tests, and rotational and visual reflex testing results were consistent with peripheral labyrinthine dysfunction. The findings of a SPECT brain scan were consistent with small ischemic insults in both the right and left cerebral hemispheres.

In another case report, a worker with inhalation and dermal exposure to solvents containing 100% 2-butanone for approximately 2 years reported dizziness, asthenia, anorexia, and weight loss (Orti-Pareja et al. 1996). Neurologic examination showed postural and action tremor in the hands, face, tongue, and voice; multifocal myoclonic jerks in the limbs; ocular flutter; and ataxic gait. Exposure levels were not reported.

Neurological examinations were conducted on 63 control workers and 41 workers at a cable factory that prepared a lacquer containing 2-butanone and (Mitran et al. 1997). The exposure-level range throughout an 8-hour shift was 149–342 mg/m^3 (50.8–117 ppm), which is entirely within accepted occupational exposure limits (OSHA 2009). Increases in several neurological symptoms, including mood disorder, irritability, memory difficulties, sleep disturbances, and headaches, were observed. In motor nerve conduction velocity tests, significant increases in proximal latency in the median, ulnar, and peroneal nerves and distal latency in the median and ulnar nerves were observed; significant decreases in nerve conduction velocity in median, ulnar, and peroneal nerves were also observed. Although the EPA IRIS on acetone (EPA 2002) and a letter to the editor (Graham 2000) cite concerns with the 1997 Mitran study, these concerns pertain particularly to the appropriateness of using that study to establish an RfC or modify health guidance values.

A study of four groups of shoe-production workers (leather, rubber or plastic workers, and tailors used as controls) was designed to assess respiratory tract toxicity associated with 2-butanone exposure (Oleru and Onyekwere 1992). Study findings reported statistically significant increases in the odds ratio for headache, chest pain, sleep disorder, dizziness, and drowsiness for workers exposed to 2-butanone as compared to controls. No information on exposure concentrations was provided.

2.2.1.5 Developmental Effects

Groups of 33 pregnant Swiss mice were exposed to 0, 400, 1,000, or 3,000 ppm 2-butanone for 7 hours per day on gestation days 6–15; weights were measured on gestation days 0, 6, 9, 15 and 18 and the dams were euthanized on gestation day 18 (Schwetz et al. 1991). No significant alterations in maternal body weight gain were observed with 2-butanone exposure, but a significant increase in relative liver weight

was observed at 3,000 ppm. A small but statistically significant decrease in fetal body weight (approximately 4% lower than controls) was observed only in the male offspring of mice exposed to 3,000 ppm. A similar but slightly smaller decrease in fetal body weight was also observed in females, but the weights were not statistically significantly different from those of controls. No significant alterations in the number of fetuses or litters with malformations were found; however, a significant trend for increased incidence of misaligned sternebrae was observed at doses >400 ppm.

Groups of 19 to 23 pregnant Sprague-Dawley rats were exposed to 0, 1,000, 2,000, 4,000, or 6,000 ppm 2-butanone 6 hours per day on gestation days 6–20 (Saillenfait et al. 2006). Significant decreases in maternal body weight gain (recorded on gestation day 0, 6, 13 and 21) and food consumption (measured across gestation days 6-13 and 13-21) were observed at exposure levels of 4,000 and 6,000 ppm. Decreases in fetal body weight were observed at ≥2,000 ppm; fetal body weights were 4.4, 15, and 20% lower than the weights of controls in the 2,000, 4,000, and 6,000 ppm groups, respectively. No significant alterations in the total number of external, visceral, or skeletal variations were observed at any level of 2-butanone exposure. However, the study reported statistically significant increases in the incidence of incomplete sternebrae ossification in the 4,000 and 6,000 ppm groups.

2.3 TOXICOKINETICS

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Blood 2-butanone levels were monitored in two subjects exposed to 25, 200, and 400 ppm on separate days for 4 hours each time (Liira et al. 1990), with monitoring continuing for 8 hours. 2-butanone blood levels increased continuously with increasing 2-butanone exposure concentrations. However, the increase

was steeper at the 200 and 400 ppm concentrations, compared with the 25-ppm concentration, where metabolic saturation appeared to occur after approximately 4 hours. Using physiologically based pharmacokinetic (PBPK) model simulations for 8-hour exposures, the investigators estimated that metabolic saturation would occur at 100 ppm at rest and at 50 ppm during exercise.

In a study developing a PBPK model in rats, a blood:gas partition coefficient of 138±15 was determined (Thrall et al. 2002).

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

No updated data.

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to 2-Butanone

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	No	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	200 ppm	ACGIH 2008
	TLV-basis (critical effect)	Upper respiratory tract irritation, central and peripheral nervous system impairment	
NIOSH	REL (10-hour TWA)	200 ppm (590 mg/m^3)	NIOSH 2005
	ST	300 ppm (885 mg/m^3)	
	IDLH	3,000 ppm	
	Target organs	Eyes, skin, respiratory system, central	

Table 7-1. Regulations and Guidelines Applicable to 2-Butanone

Agency	Description	Information	Reference
		nervous system	
OSHA	PEL (8-hour TWA) for general industry	200 ppm (590 mg/m^3)	OSHA 2009
NATIONAL *(cont.)*			
b. Water			
EPA	Drinking water standards and health advisories		EPA 2006
	1-day health advisory for a 10-kg child	75 mg/L	
	10-day health advisory for a 10-kg child	7.5 mg/L	
	DWEL	20 mg/L	
	Lifetime	4 mg/L	
	10^{-4} Cancer risk	No	
	National primary drinking water standards	No	EPA 2009
c. Other			
ACGIH	Carcinogenicity classification	No	ACGIH 2008
	Biological exposure indices (end of shift)		
	Methyl ethyl ketone in urine	2 mg/L	

Table 7-1. Regulations and Guidelines Applicable to 2-Butanone

Agency	Description	Information	Reference
EPA	Carcinogenicity classification	No	IRIS 2009
	RfC	5 mg/m^3	
	RfD	0.6 mg/kg-day	
NTP	Carcinogenicity classification	No	NTP 2005

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

8. REFERENCES

ACGIH. 2008. 2008 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, pages 40 and 106.

Callender TJ. 1995. Neurotoxic impairment in a case of methylethyl-ketone exposure. Arch Environ Health 50(5):392. http://www.ncbi.nlm.nih.gov/pubmed/7574898.

Dick RB, Krieg EF, Jr., Setzer J, et al. 1992. Neurobehavioral effects from acute exposures to methyl

isobutyl ketone and methyl ethyl ketone. Fundam Appl Toxicol 19(3):453–473. http://www.ncbi.nlm.nih.gov/pubmed/1459376.

EPA. 2002. Toxicological Review of Acetone. EPA/635/R-03/004. http://www.epa.gov/iris/toxreviews/0128tr.pdf June 30, 2010.

EPA. 2003. Toxicological Review of Methyl Ethyl Ketone. EPA 635/R-03/009. http://www.epa.gov/ncea/iris/toxreviews/0071tr.pdf. June 30, 2010.

EPA. 2009. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency. Office of Ground Water and Drinking Water. EPA816F09004. http://www.epa.gov/safewater/consumer/pdf/mcl.pdf. August 7, 2009.

EPA. 2006. 2006 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. Office of Water. EPA822R04005. http://epa.gov/waterscience/criteria/drinking/dwstandards.pdf. May 19, 2009.

Graham, DG. (2000) [Letter to the editor: Critical analysis of Mitran et al. (1997). Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone, and cyclohexane. Environ. Res. 73: 181-188]. Environ. Res. 82:181–183.

IARC. 2009. Agents reviewed by the IARC Monographs. Volumes 1-100A. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/ListagentsCASnos.pdf. May 19, 2009.

IRIS. 2009. Methyl ethyl ketone (MEK). Integrated Risk Information System. Washington, DC: U.S.

Environmental Protection Agency. http://www.epa.gov/ncea/iris/subst/0071.htm. August 6, 2009.

Liira J, Johanson G, Riihimaki V. 1990. Dose-dependent kinetics of inhaled methylethylketone in man. Toxicol Lett 50(2-3):195–201. http://www.ncbi.nlm.nih.gov/pubmed/2309238.

Mitran E, Callender T, Orha B, et al. 1997. Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone, and cyclohexanone. Environ Res 73(1-2):181–188. http://www.ncbi.nlm.nih.gov/pubmed/9311545.

Muttray A, Jung D, Klimek L, et al. 2002. Effects of an external exposure to 200 ppm methyl ethyl ketone on nasal mucosa in healthy volunteers. Int Arch Occup Environ Health 75(3):197–200. http://www.ncbi.nlm.nih.gov/pubmed/11954988.

NIOSH. 2005. 2-Butanone. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health. Centers for Disease Control and Prevention. NIOSH Publication 2005–149. http://www.cdc.gov/niosh/npg/npgd0069.html. August 6, 2009.

NTP. 2005. Report on carcinogens, eleventh edition. Research Triangle Park, NC: U.S. Department of Health and Human Services. Public Health Service. National Toxicology Program. http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. January 11, 2008.

Oleru UG, Onyekwere C. 1992. Exposures to polyvinyl chloride, methyl ketone and other chemicals. The pulmonary and non-pulmonary effect. Int Arch Occup Environ Health 63(7):503–507. http://www.ncbi.nlm.nih.gov/pubmed/1577530.

Orti-Pareja M, Jimenez-Jimenez FJ, Miquel J, et al. 1996. Reversible myoclonus, tremor, and ataxia in a

patient exposed to methyl ethyl ketone. Neurology 46(1):272. http://www.ncbi.nlm.nih.gov/pubmed/8559401.

OSHA. 2009. Table Z-1 limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000 Subpart Z. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992. May 19, 2009.

Saillenfait AM, Gallissot F, Sabate JP, et al. 2006. Developmental toxicity of combined ethylbenzene and methylethylketone administered by inhalation to rats. Food Chem Toxicol 44(8):1287–1298. http://www.ncbi.nlm.nih.gov/pubmed/16624470.

Schwetz BA, Mast TJ, Weigel RJ, et al. 1991. Developmental toxicity of inhaled methyl ethyl ketone in Swiss mice. Fundam Appl Toxicol 16(4):742–748. http://www.ncbi.nlm.nih.gov/pubmed/1884913.

Thrall KD, Soelberg JJ, Weitz KK, et al. 2002. Development of a physiologically based pharmacokinetic model for methyl ethyl ketone in F344 rats. J Toxicol Environ Health A 65(13):881–896. http://www.ncbi.nlm.nih.gov/pubmed/12133235.

WHO. 2000. Summary of the guidelines. In: WHO air quality guidelines for Europe. 2nd ed. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/document/aiq/3summary.pdf. May 19, 2009.

WHO. 2006. Annex 4 - Chemical summary tables. In: Guidelines for drinking-water quality, third edition, incorporating first and second addenda. Geneva, Switzerland: World Health Organization, 488–492. http://www.who.int/water_sanitation_health/dwq/GDWAN4rev1and2.pdf. May 19, 2009.