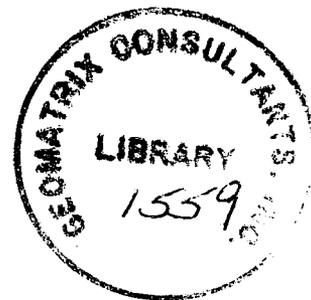


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DOCUMENTATION OF THE THRESHOLD LIMIT VALUES AND BIOLOGICAL EXPOSURE INDICIES

Sixth Edition

1991



American Conference of Governmental Industrial Hygienists, Inc.
Cincinnati, Ohio _____



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Introduction

This sixth edition of the Documentation of the Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) presents the basic rationale for the establishment of occupational exposure values for 626 chemical substance entries and 13 physical agents; data on BEIs are provided for 26 substances, all of which are listed in the 1991–1992 *Threshold Limit Values and Biological Exposure Indices Booklet*.

These values are intended for use in the practice of industrial hygiene as guidelines or recommendations in the control of potential health hazards and for no other use, e.g., in the evaluation or control of community air pollution or physical agent nuisances; in estimating the toxic potential of continuous, uninterrupted exposures or other extended work periods; as proof or disproof of an existing disease or physical condition; or adoption by countries whose working conditions differ from those in the United States and where processes differ. These values are not intended as fine lines between safe and dangerous exposure concentrations or exposures to physical agents nor are they a relative index of toxicity or physical disability. They should not be used by anyone untrained in the discipline of industrial hygiene.

Chemical Substances

The Chemical Substances section of this volume is devoted to documenting the values recommended for airborne exposure concentrations of the cited substances. These values represent conditions under which it is believed nearly all workers may be repeatedly exposed day after day without adverse health effects. However, because of wide variation in individual susceptibility, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness.

TLVs are based on the best available information from industrial experience, from experimental human and animal studies, and when possible, from a combination of the three. The basis on which the values are established may differ from substance to substance; protection against impairment of health may be a guiding factor for some, whereas reasonable freedom from irritation, narcosis, nuisance, or other forms of stress may form the basis for others.

This sixth edition of the Documentation has been revised to include a chronology that traces the events

leading to the adoption or proposed revision of the present TLV for a chemical substance. In addition, Permissible Exposure Limits (PELs) from the U.S. Occupational Safety and Health Administration (OSHA) and Recommended Exposure Limits (RELs) from the U.S. National Institute for Occupational Safety and Health (NIOSH) are presented. Values established by selected other countries are also noted. Reorganization of the data and the introduction of appropriate subheads have been undertaken to facilitate examination and review. New materials have been incorporated as available.

The substances are arranged in alphabetical order. The primary name appears first, followed by the CAS number, any synonyms for the substances, the molecular formula, and, where appropriate, the structural formula. The current TLV and any special notations (e.g., SKIN, CARCINOGEN) appear immediately before the timeline for the substance.

The TLVs are expressed as a time-weighted average (TLV–TWA), or as a Short-Term Exposure Limit (TLV–STEL), or as a Ceiling (TLV–C) Limit. These terms are defined as follows:

The TLV–TWA is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

A STEL is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV–TWA. Exposures above the TLV–TWA up to the STEL should not be longer than 15 minutes and should not occur more than four times per day. There should be at least 60 minutes between successive exposures in this range. An averaging period other than 15 minutes may be recommended when this is warranted by observed biological effects.

The TLV–C is the concentration that should not be exceeded during any part of the working exposure.

Excursion Limits. For the vast majority of substances with a TLV–TWA, there is not enough toxicological data available to warrant a STEL. Nevertheless, excursions above the TLV–TWA should be controlled even where the 8-hour TLV–TWA is within recommended limits. Excursions in worker exposure levels may exceed 3 times the TLV–TWA for no more than a total of 30 minutes during a workday, and under no circumstances should they exceed 5 times the TLV–TWA, provided that the TLV–TWA is not exceeded.

Carcinogens. Appendix A on the "Identification and

Classification of Carcinogens" provides a list of substances associated with industrial processes that are recognized to have carcinogenic or cocarcinogenic potential. For most of the substances determined to be carcinogenic by the TLV Committee, the stated value or classification is intended to provide a practical guideline for the industrial hygiene professional to assist in control of exposures in the workplace. These guidelines are not final; the Committee continues to update them as new information becomes available.

At the present time, two categories of carcinogens have been designated by the TLV Committee to recognize the qualitative differences in research results:

A1 — Confirmed Human Carcinogens. Substances, or substances associated with industrial processes, recognized to have carcinogenic potential.

A2 — Suspected Human Carcinogens. Chemical substances, or substances associated with industrial processes, which are suspect of inducing cancer, based on either limited epidemiological evidence or demonstration of carcinogenesis in one or more animal species by appropriate methods.

Generally, the text for each chemical substance has been organized under the following headings:

- Chemical and Physical Properties
- Major Uses or Sources of Occupational Exposure
- Animal Studies
- Reproductive/Developmental Studies
- Genotoxicity Studies
- Pharmacokinetic/Metabolism Studies
- Human Studies
- TLV Recommendation
- Other Recommendations
- Carcinogenic Classification
- Other Nations
- References

Physical Agents

The section on physical agents is devoted to an examination of exposure to certain physical agents in the workplace environment. As possible adverse effects of a particular physical agent are identified, the Committee reviews available data and recommends an exposure value to which it is believed nearly all workers may be repeatedly exposed without adverse health effects. These TLVs for physical agents are based on the best available information from industrial experience, from experimental human and animal studies, and whenever possible, from a combination of the three. Nevertheless, because of wide variations in individual susceptibility, exposure of an occasional individual at, or even below, the threshold limit may not prevent annoyance, aggravation of a pre-existing condition, or physiological damage.

Biological Exposure Indices

The section on Biological Exposure Indices identifies those substances for which a reference value has been developed to be used as a guideline in evaluating potential health hazards in the practice of industrial hygiene. BEIs represent the levels of determinants that are most likely to be found in biological specimens collected from a healthy worker who has been exposed to chemicals to the same extent as a worker with inhalation exposure to the chemical substance TLV.

BEIs do not represent a sharp distinction between hazardous and nonhazardous exposures. Due to biological variability, it is possible for an individual's measurements to exceed the BEI without incurring an increased health risk. If, however, measurements in specimens obtained from a worker on different occasions persistently exceed the BEI, or if the majority of measurements in specimens obtained from a group of workers at the same workplace exceed the BEI, the cause of the excessive values must be investigated and proper action taken to reduce the exposure.

The "Introduction" to the BEI section of this volume provides additional important information regarding the development and application of these values.

Policy on Use of TLVs and BEIs

The reader of this Documentation volume is strongly advised to bear in mind that the values and documentations presented herein are designed for use in the practice of industrial hygiene by a qualified professional. They are designed as guidelines or recommendations in the control of potential health hazards and should not be used in any other application.

The reader should review the following "Policy Statement on the Uses of TLVs and BEIs" issued by the Board of Directors of the American Conference of Governmental Industrial Hygienists on March 1, 1988.

"The Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) are developed as guidelines to assist in the control of health hazards. These recommendations or guidelines are intended for use in the practice of industrial hygiene, to be interpreted and applied only by a person trained in this discipline. They are not developed for use as legal standards, and the American Conference of Governmental Industrial Hygienists (ACGIH) does not advocate their use as such. However, it is recognized that in certain circumstances individuals or organizations may wish to make use of these recommendations or guidelines as a supplement to their occupational safety and health program. The ACGIH will not oppose their use in this manner, if the use of TLVs and BEIs in these instances will contribute to the overall improvement in worker protection. However, the user must recognize the constraints and limitations subject to their proper use and bear the responsibility for such use.

"The Introductions to the TLV/BEI booklet and the TLV/BEI Documentation provide the philosophical and practical bases for the uses and limitations of the TLVs and BEIs. To extend those uses of the TLVs and BEIs to include other applications, such as use without the judgment of an industrial hygienist, application to a different population, development of new exposure/recovery time models, or new effect endpoints, stretch the reliability and

even viability of the data base for the TLV or BEI as evidenced by the individual documentations.

"It is not appropriate for individuals or organizations to impose on the TLVs or the BEIs their concepts of what the TLVs or BEIs should be or how they should be applied or to transfer regulatory standards requirements to the TLVs or BEIs."

DOCUMENTATION OF THE THRESHOLD LIMIT VALUES

**For Chemical Substances
in the
Work Environment**

Contents

A		
Acetaldehyde [75-07-0]	Supplement	
Acetic Acid [64-19-7]	6	
Acetic Anhydride [108-24-7]	8	
Acetone [67-64-1]	10	
Acetone Cyanohydrin [75-86-5]	Supplement	
Acetonitrile [75-05-8]	12	
Acetophenone [98-86-2]	Supplement	
Acetylene [74-86-2]	15	
Acetylene Tetrabromide [79-27-6]	18	
Acetylsalicylic Acid (Aspirin) [50-78-2]	20	
Acrolein [107-02-8]	21	
Acrylamide [79-06-1]	23	
Acrylic Acid [79-10-7]	26	
Acrylonitrile [107-13-1]	30	
Adipic Acid [124-04-9]	Supplement	
Adiponitrile [111-69-3]	Supplement	
Aldrin [309-00-2]	33	
Allyl Alcohol [107-18-6]	35	
Allyl Chloride [107-05-1]	37	
Allyl Glycidyl Ether (AGE) [106-92-3]	43	
Allyl Propyl Disulfide [2179-59-1]	45	
Aluminum [7429-90-5]	46	
Aluminum Oxide [1344-28-1]	48	
4-Aminodiphenyl [92-67-1]	50	
2-Aminopyridine [504-29-0]	52	
Amitrole [61-82-5]	54	
Ammonia [7664-41-7]	58	
Ammonium Chloride Fume [12125-02-9]	60	
Ammonium Perfluorooctanoate [3825-26-1]	Supplement	
Ammonium Sulfamate [7773-06-0]	63	
n-Amyl Acetate [628-63-7]	65	
sec-Amyl Acetate [626-38-0]	66	
Aniline and Homologues [62-53-3]	68	
Anisidine [29191-52-4]	71	
Antimony and Compounds [7440-36-0]	73	
Antimony Trioxide [1309-64-4]	76	
ANTU [86-88-4]	79	
Argon [7440-37-1]	81	
Arsenic, Elemental [7440-38-2] and Inorganic Compounds (Except Arsine)	Supplement	
Arsenic Trioxide Production [1327-53-3]	85	
Arsine [7784-42-1]	87	
Asbestos [1332-21-4]	89	
Asphalt (Petroleum) Fumes [8052-42-4]	95	
Atrazine [1912-24-9]	97	
Azinphos-Methyl [86-50-0]	100	
B		
Barium [7440-39-3]	102	
Barium Sulfate [7727-43-7]	104	
Benomyl [17804-35-2]	106	
Benz[a]anthracene [56-55-3]	Supplement	
Benzene [71-43-2]	108	
Benzidine [92-87-5]	121	
Benzo[b]fluoranthene [205-99-2]	Supplement	
Benzoyl Chloride [98-88-4]	Supplement	
Benzoyl Peroxide [94-36-0]	123	
Benzo[a]pyrene [50-32-8]	125	
Benzyl Acetate [140-11-4]	Supplement	
Benzyl Chloride [100-44-7]	132	
Beryllium and Compounds [7440-41-7]	134	
Biphenyl [92-52-4]	137	
Bismuth Telluride [1304-82-1]	139	
Borates, Tetra, Sodium Salts [1303-96-4]	141	
Boron Oxide [1303-86-2]	143	
Boron Tribromide [10294-33-4]	145	
Boron Trifluoride [7637-07-2]	146	
Bromacil [314-40-9]	148	
Bromine [7726-95-6]	Supplement	
Bromine Pentafluoride [7789-30-2]	152	
Bromoform [75-25-2]	154	
1,3-Butadiene [106-99-0]	Supplement	
Butane [106-97-8]	160	
tert-Butanol [75-65-0]	Supplement	
2-Butoxyethanol (EGBE) [111-76-2]	162	
n-Butyl Acetate [123-86-4]	Supplement	
sec-Butyl Acetate [105-46-4]	166	
tert-Butyl Acetate [540-88-5]	167	
n-Butyl Acrylate [141-32-2]	168	
n-Butyl Alcohol [71-36-3]	170	
sec-Butyl Alcohol [78-92-2]	172	
tert-Butyl Alcohol [75-65-0]	174	
n-Butylamine [109-73-9]	176	
tert-Butyl Chromate [1189-85-1]	178	
n-Butyl Glycidyl Ether (BGE) [2426-08-6]	180	
n-Butyl Lactate [138-22-7]	182	

2-N-Dibutylaminoethanol [102-81-8]	Supplement	Dioxane [123-91-1]	512
Dibutyl Phenyl Phosphate [2528-78-1]	397	Dioxathion [78-34-2]	516
Dibutyl Phosphate [107-66-4]	399	Diphenylamine [122-39-4]	518
Dibutyl Phthalate [84-74-2]	400	Dipropylene Glycol Methyl Ether [34590-94-8]	520
Dichloroacetylene [7572-29-4]	Supplement	Dipropyl Ketone [123-19-3]	522
o-Dichlorobenzene [95-50-1]	Supplement	Diquat [2764-72-9]	Supplement
p-Dichlorobenzene [106-46-7]	Supplement	Di-sec-octyl Phthalate [117-81-7]	528
3,3'-Dichlorobenzidine [91-94-1]	417	Disulfiram [97-77-8]	532
1,4-Dichloro-2-butene [764-41-0]	Supplement	Disulfoton [298-04-4]	534
Dichlorodifluoromethane [75-71-8]	420	2,6-Di-tert-butyl-p-cresol [128-37-0]	536
1,3-Dichloro-5,5-dimethyl Hydantoin [118-52-5]	423	Diuron [330-54-1]	538
1,1-Dichloroethane [75-34-3]	Supplement	Divinyl Benzene [1321-74-0]	540
1,2-Dichloroethylene [540-59-0]	429		
Dichloroethyl Ether [111-44-4]	432	E	
Dichlorofluoromethane [75-43-4]	434	Emery [1302-74-5]	543
1,1-Dichloro-1-nitroethane [594-72-9]	436	Endosulfan [115-29-7]	544
1,3-Dichloropropene [542-75-6]	438	Endrin [72-20-8]	546
2,2-Dichloropropionic Acid [75-99-0]	441	Enflurane [13838-16-9]	548
Dichlorotetrafluoroethane [76-14-2]	443	Epichlorohydrin [106-89-8]	550
Dichlorvos [62-73-7]	446	EPN [2104-64-5]	Supplement
Dicrotophos [141-66-2]	449	Ethane [74-84-0]	559
Dicyclopentadiene [77-73-6]	451	Ethanolamine [141-43-5]	560
Dicyclopentadienyl Iron [102-54-5]	453	Ethion [563-12-2]	562
Dieldrin [60-57-1]	455	2-Ethoxyethanol (EGEE) [110-80-5]	564
Diethanolamine [111-42-2]	Supplement	2-Ethoxyethyl Acetate (EGEEA) [111-15-9]	567
Diethylamine [109-89-7]	Supplement	Ethyl Acetate [141-78-6]	569
2-Diethylaminoethanol [100-37-8]	Supplement	Ethyl Acrylate [140-88-5]	571
Diethylene Triamine [111-40-0]	464	Ethyl Alcohol [64-17-5]	575
Diethyl Ketone [96-22-0]	466	Ethylamine [75-04-7]	Supplement
Diethyl Phthalate [84-66-2]	467	Ethyl Amyl Ketone [541-85-5]	579
Difluorodibromomethane [75-61-6]	469	Ethyl Benzene [100-41-4]	581
Diglycidyl Ether (DGE) [2238-07-5]	471	Ethyl Bromide [74-96-4]	Supplement
Diisobutyl Ketone [108-83-8]	473	Ethyl Butyl Ketone [106-35-4]	592
Diisopropylamine [108-18-9]	475	Ethyl Chloride [75-00-3]	Supplement
Dimethyl Acetamide [127-19-5]	477	Ethylene [74-85-1]	598
Dimethylamine [124-40-3]	Supplement	Ethylene Chlorohydrin [107-07-3]	600
Dimethylaniline [121-69-7]	482	Ethylenediamine [107-15-3]	603
Dimethyl Carbamoyl Chloride [79-44-7]	486	Ethylene Dibromide [106-93-4]	606
Dimethylethoxysilane [14857-34-2]	Supplement	Ethylene Dichloride [107-06-2]	609
Dimethylformamide [68-12-2]	488	Ethylene Glycol [107-21-1]	Supplement
1,1-Dimethylhydrazine [57-14-7]	Supplement	Ethylene Glycol Dinitrate [628-96-6]	614
Dimethylphthalate [131-11-3]	495	Ethylene Oxide [75-21-8]	617
Dimethyl Sulfate [77-78-1]	497	Ethylenimine [151-56-4]	628
Dinitolmide [148-01-6]	500	Ethyl Ether [60-29-7]	631
Dinitrobenzene [528-29-0; 99-65-0; 100-25-4]	502	Ethyl Formate [109-94-4]	633
Dinitro-o-cresol [534-52-1]	504	Ethylidene Norbornene [16219-75-3]	635
Dinitrotoluene [25321-14-6]	Supplement	Ethyl Mercaptan [75-08-1]	636
		N-Ethylmorpholine [100-74-3]	638

M

Magnesite [546-93-0]	867	4,4'-Methylene Dianiline [101-77-9]	998
Magnesium Oxide Fume [1309-48-4]	869	Methyl Ethyl Ketone [78-93-3]	1002
Malathion [121-75-5]	871	Methyl Ethyl Ketone Peroxide [1338-23-4]	1005
Maleic Anhydride [108-31-6]	874	Methyl Formate [107-31-3]	1007
Manganese, Elemental and Inorganic Compounds [7439-96-5]	Supplement	Methyl Hydrazine [60-34-4]	Supplement
Manganese Cyclopentadienyl Tricarbonyl [12079-65-1]	879	Methyl Iodide [74-88-4]	1013
Mercury, All Forms Except Alkyl [7439-97-6]	Supplement	Methyl Isoamyl Ketone [110-12-3]	1015
Mercury, Alkyl Compounds	893	Methyl Isobutyl Carbinol [108-11-2]	1017
Mesityl Oxide [141-79-7]	896	Methyl Isobutyl Ketone [108-10-1]	1019
Methacrylic Acid [79-41-4]	899	Methyl Isocyanate [624-83-9]	1022
Methane [74-82-8]	901	Methyl Isopropyl Ketone [563-80-4]	1025
Methanol [67-56-1]	903	Methyl Mercaptan [74-93-1]	1026
Methomyl [16752-77-5]	906	Methyl Methacrylate [80-62-6]	1029
Methoxychlor [72-43-5]	909	Methyl Parathion [298-00-0]	1034
2-Methoxyethanol [109-86-4]	913	Methyl Propyl Ketone [107-87-9]	1036
2-Methoxyethyl Acetate [110-49-6]	922	Methyl Silicate [681-84-5]	1038
4-Methoxyphenol [150-76-5]	925	α -Methyl Styrene [98-83-9]	1040
Methyl Acetate [79-20-9]	927	Metribuzin [21087-64-9]	1042
Methyl Acetylene [74-99-7]	929	Mevinphos [7786-34-7]	1044
Methyl Acetylene-Propadiene Mixture	930	Mica [12001-26-2]	1047
Methyl Acrylate [96-33-3]	931	Mineral or Rock Wool	1049
Methylacrylonitrile [126-98-7]	935	Molybdenum and Compounds [7439-98-7]	1051
Methylal [109-87-5]	937	Monocrotophos [6923-22-4]	1055
Methylamine [74-89-5]	939	Morpholine [110-91-8]	1058
Methyl n-Amyl Ketone [110-43-0]	941	N	
n-Methyl Aniline [100-61-8]	943	Naled [300-76-5]	1061
Methyl Bromide [74-83-9]	945	Naphthalene [91-20-3]	1063
Methyl tert-Butyl Ether [1634-04-4]	Supplement	β -Naphthylamine [91-59-8]	1067
Methyl n-Butyl Ketone [591-78-6]	949	Neon [7440-01-9]	1069
Methyl Chloride [74-87-3]	953	Nickel and Inorganic Compounds [7440-02-0]	1070
Methyl Chloroform [71-55-6]	958	Nickel Carbonyl [13463-39-3]	1076
Methyl 2-Cyanoacrylate [137-05-3]	965	Nickel Sulfide Roasting	1079
Methylcyclohexane [108-87-2]	967	Nicotine [54-11-5]	1083
Methylcyclohexanol [25639-42-3]	969	Nitrapyrin [1929-82-4]	1086
o-Methylcyclohexanone [583-60-8]	971	Nitric Acid [7697-37-2]	1088
2-Methylcyclopentadienyl Manganese Tricarbonyl [12108-13-3]	973	Nitric Oxide [10102-43-9]	1090
Methyl Demeton [8022-00-2]	975	p-Nitroaniline [100-01-6]	1093
Methylene Bisphenyl Isocyanate [101-68-8]	978	Nitrobenzene [98-95-3]	1096
Methylene Chloride [75-09-2]	981	p-Nitrochlorobenzene [100-00-5]	1100
4,4'-Methylene bis(2-Chloroaniline) [101-14-4]	Supplement	4-Nitrodiphenyl [92-93-3]	1103
Methylene bis-(4-Cyclohexylisocyanate) [5124-30-1]	996	Nitroethane [79-24-3]	1105
		Nitrogen [7727-37-9]	1107
		Nitrogen Dioxide [10102-44-0]	1108
		Nitrogen Trifluoride [7783-54-2]	1111
		Nitroglycerin [55-63-0]	1113
		Nitromethane [75-52-5]	Supplement

Rubber Solvent	1352	Talc [14807-96-6]	1480
S			
Selenium and Compounds [7782-49-2]	1354	Tantalum [7440-25-7]	
Selenium Hexafluoride [7783-79-1]	1361	Metal and Oxide [1314-61-0]	1487
Sesone [136-78-7]	1363	Tellurium and Compounds [13494-80-9]	1489
Silica, Amorphous—Diatomaceous Earth		Tellurium Hexafluoride [7783-80-4]	1492
[61790-53-2]	Supplement	Temephos [3383-96-8]	1494
Silica, Amorphous—Fume [69012-64-2]	1367	TEPP [107-49-3]	1497
Silica, Amorphous—Fused [60676-86-0]	1371	Terephthalic Acid [100-21-0]	Supplement
Silica, Amorphous—Precipitated and Gel		Terphenyls [26140-60-3]	1499
[112926-00-8]	1373	1,1,1,2-Tetrachloro-2,2-difluoroethane	
Silica, Crystalline—Cristobalite [14464-46-1]	1375	[76-11-9]	1502
Silica, Crystalline—Quartz [14808-60-7]	1377	1,1,2,2-Tetrachloro-1,2-difluoroethane	
Silica, Crystalline—Tridymite [15468-32-3]	1383	[76-12-0]	1504
Silica, Crystalline—Tripoli [1317-95-9]	1385	1,1,2,2-Tetrachloroethane [79-34-5]	1506
Silicon [7440-21-3]	1387	Tetrachloronaphthalene [1335-88-2]	1511
Silicon Carbide [409-21-2]	1389	Tetraethyl Lead [78-00-2]	1513
Silicon Tetrahydride [7803-62-5]	1394	Tetrahydrofuran [109-99-9]	1517
Silver and Compounds [7440-22-4]	1396	Tetramethyl Lead [75-74-1]	1521
Soapstone	1401	Tetramethyl Succinonitrile [3333-52-6]	1524
Sodium Azide [26628-22-8]	1403	Tetranitromethane [509-14-8]	Supplement
Sodium Bisulfite [7631-90-5]	1408	Tetrasodium Pyrophosphate [7722-88-5]	1529
Sodium Fluoroacetate [62-74-8]	Supplement	Tetryl [479-45-8]	1531
Sodium Hydroxide [1310-73-2]	1416	Thallium [7440-28-0]	1534
Sodium Metabisulfite [7681-57-4]	1418	4,4-Thiobis(6-tert-butyl-m-cresol) [96-69-5]	1538
Starch [9005-25-8]	1420	Thioglycolic Acid [68-11-1]	1541
Stearates	1422	Thionyl Chloride [7719-09-7]	1543
Stibine [7803-52-3]	1426	Thiram [137-26-8]	1545
Stoddard Solvent [8052-41-3]	1428	Tin, Metal, Oxide, and Inorganic Compounds	
Strontium Chromate [7789-06-2]	1431	[7440-31-5]	1550
Strychnine [57-24-9]	1433	Tin, Organic	1552
Styrene, Monomer [100-42-5]	1436	Titanium Dioxide [13463-67-7]	1561
Subtilisins [1395-21-7; 9014-01-1]	1447	o-Tolidine [119-93-7]	1564
Sucrose [57-50-1]	1449	Toluene [108-88-3]	1568
Sulfometuron Methyl [74222-97-2]	Supplement	Toluene-2,4-diisocyanate [584-84-9]	1581
Sulfotep [3689-24-5]	1452	o-Toluidine [95-53-4]	1590
Sulfur Dioxide [7446-09-5]	1455	m-Toluidine [108-44-1]	1595
Sulfur Hexafluoride [2551-62-4]	1459	p-Toluidine [106-49-0]	1597
Sulfuric Acid [7664-93-9]	1461	Tributyl Phosphate [126-73-8]	1600
Sulfur Monochloride [10025-67-9]	1464	Trichloroacetic Acid [76-03-9]	1602
Sulfur Pentafluoride [5714-22-7]	1466	1,2,4-Trichlorobenzene [120-82-1]	1605
Sulfur Tetrafluoride [7783-60-0]	1468	1,1,2-Trichloroethane [79-00-5]	1607
Sulfuryl Fluoride [2699-79-8]	1470	Trichloroethylene [79-01-6]	Supplement
Sulprofos [35400-43-2]	1473	Trichlorofluoromethane [75-69-4]	1619
T			
2,4,5-T [93-76-5]	1476	Trichloronaphthalene [1321-65-9]	1624
		1,2,3-Trichloropropane [96-18-4]	1626
		1,1,2-Trichloro-1,2,2-trifluoroethane	
		[76-13-1]	1631
		Triethanolamine [102-71-6]	Supplement

BUTANE

CAS: 106-97-8 (n-Butane)

CAS: 75-28-5 (Isobutane)

n-Butane; Methylene methane; 2-Methylpropane (isobutane)

C₄H₁₀

TLV-TWA, 800 ppm (1900 mg/m³)

1971-1972: TLV-TWA, none, Simple Asphyxiants (SA) Appendix

1971: TLV-TWA, 500 ppm, proposed

1973-1975: TLV-TWA, 500 ppm, SA Appendix

1974: TLV-TWA, 600 ppm, proposed

1976-1980: TLV-TWA, 600 ppm, SA Appendix

1976-1980: TLV-STEL, 750 ppm

1979: TLV-TWA, 800 ppm, proposed

1981: Deleted from SA Appendix

1981: TLV-STEL, deleted

1981-present: TLV-TWA, 800 ppm

1991: Documentation revised

Chemical and Physical Properties

Butane consists of two isomers, n-butane [CH₃CH₂CH₂CH₃] and isobutane [(CH₃)₃CH]. They are colorless, flammable gases. n-Butane has a natural gas odor and isobutane, a slight odor. Reportedly, the odor of butane is not recognized in air below 50,000 ppm.⁽¹⁾

Chemical and physical properties of the isomers include:

Molecular weight: 58.12

Density: 0.5788 (n-); 0.5572 (iso-) at 20°C

Freezing point: -138.35°C (n-); -159.6°C (iso-)

Boiling point: -0.5°C (n-); -11.7°C (iso-)

Closed cup flash point: -60°C (n-); -82.8°C (iso-)

Vapor density: 2.07 (air = 1.0)

Explosive limits: upper, 8.4%; lower, 1.9% (both isomers)

Autoignition temperature: 405°C (n-); 462°C (iso-)

Solubility: soluble in water; very soluble in alcohol, ether, and chloroform (both isomers)

Major Uses or Sources of Occupational Exposure

Both isomers of butane are used as components of aerosol propellants and as fuel sources. Both isomers occur in natural gas and are in liquefied petroleum gas (LPG). n-Butane is used as a chemical feedstock for special chemicals in the solvent, rubber, and plastics industries. Isobutane is used as a raw material for petrochemicals and an industrial carrier gas. Isobutane is a raw material in the chemical industry for the production of propylene glycols and oxides and polyurethane foams and resins.

Animal Studies

Acute

The 4-hour LC₅₀ for n-butane for rats is 658 g/m³ or about 280,000 ppm.⁽²⁾ n-Butane is anesthetic to mice at 13% (130,000 ppm) in 25 minutes and at 22% (220,000 ppm) in 1 minute.⁽¹⁾ In the dog, 25% (250,000 ppm) n-butane was required for anesthesia.⁽¹⁾ In guinea pigs, n-butane at concentrations of 2.1%-5.6% (21,000-56,000 ppm) caused sniffing and chewing movements with a rapid rate of breathing. The animals recovered quickly after cessation of exposure.⁽¹⁾ n-Butane is reported to be a weak cardiac sensitizer in the dog,⁽¹⁾ and 5000 ppm in the anesthetized dog may cause hemodynamic changes, such as a decreased cardiac output, decreases in left ventricular pressure and stroke volume, and decreases in myocardial contractibility and aortic pressure.

The 1-hour LC₅₀ for isobutane for the mouse is 52 mg/kg.⁽¹⁾ Near the LC₅₀, mice exhibited central nervous system (CNS) depression, rapid and shallow respiration, and apnea. Isobutane may also be a cardiac sensitizer.⁽¹⁾ In the anesthetized dog, there were no significant effects up to 2% (20,000 ppm) isobutane, but there were significant hemodynamic changes from 2.5% through 10%.⁽¹⁾ In the dog, anesthesia occurs at 45% (450,000 ppm) after 10 minutes exposure to isobutane.⁽¹⁾

Human Studies

A 10-minute exposure at 10,000 ppm (1%) butane gas results in drowsiness, but no other evidence of systemic effects.⁽¹⁾ Stewart et al.⁽³⁾ found no untoward subjective or abnormal physiological responses in human subjects exposed to isobutane for single 8-hour periods at 1000 ppm, or 8 hours/day, 5 days/week at 500 ppm for 2 weeks. During the second week of exposure at 500 ppm, however, a reduction in the visual evoked response (VER) wave amplitude was observed. The significance of this finding was considered to be uncertain.

TLV Recommendation

Butane, like other homologues in the straight chain, saturated, aliphatic hydrocarbon series (pentane, hexane), is not characterized by its toxicity, but rather by its narcosis-producing potential at high exposure levels. There were no reports available indicating that butane is significantly irritating at moderate levels of exposure. Therefore, the recommended TLV is based on analogy with that of pentane by comparing their lower explosive limits in air. Thus, a TLV-TWA of 800 ppm is recommended for n-butane and isobutane. On a weight basis, the limit for butane is somewhat higher, a relationship consistent with the relative toxicities. At this time, no STEL is suggested until additional toxicological data and

industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 800 ppm for butane. OSHA concluded that this limit would protect workers against the significant risks of drowsiness and other narcotic effects. The OSHA PEL is consistent with the TLV-TWA recommendation.⁽⁴⁾

NIOSH REL/IDLH: NIOSH has established a REL-TWA of 800 ppm for butane [NIOSH, Ex 8-47, Table N1] by concurrence with the OSHA PEL.⁽⁴⁾ NIOSH has not established an IDLH value for this substance.

NTP Studies: n-Butane was negative in the *Drosophila* sex-linked recessive lethal/reciprocal translocation tests and is on test for *Salmonella* genetic toxicity. Cyto-

genetic tests and *in vivo* toxicity studies have been deferred.

Other Nations

Australia: 800 ppm (1990); Federal Republic of Germany: 1000 ppm, short-term level 2000 ppm, 60 minutes, 3 times per shift (both isomers) (1990); United Kingdom: 600 ppm, 10-minute STEL, 750 ppm (1991).

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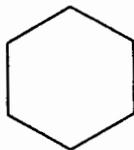
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CYCLOHEXANE

CAS: 110-82-7

Hexahydrobenzene; Hexamethylene; Hexanaphthalene

C₆H₁₂



TLV-TWA, 300 ppm (1030 mg/m³)

1946-1947: MAC-TWA, 400 ppm

1948-1964: TLV-TWA, 400 ppm

1965: TLV-TWA, 300 ppm, proposed

1967-present: TLV-TWA, 300 ppm

1976-1986: TLV-STEL, 375 ppm

1987: TLV-STEL, deleted

1991: Documentation revised

Chemical and Physical Properties

Cyclohexane is a colorless, mobile liquid with a pungent odor. The reported odor threshold is approximately 25 ppm.⁽¹⁾ Cyclohexane is a dangerous fire hazard. Chemical and physical properties include:⁽²⁾

Molecular weight: 84.16

Specific gravity: 0.779 at 20°C

Freezing point: 6.47°C

Boiling point: 80.7°C

Vapor pressure: 95 torr at 20°C

Flammability limits: upper, 7.75%; lower, 1.26% by volume in air

Closed cup flash point: -18°C (98% grade)

Autoignition temperature: 260°C

Solubility: insoluble in water; soluble in acetone, alcohol, and benzene

Major Uses or Sources of Occupational Exposure

Cyclohexane is used as a paint and varnish remover; as a solvent for lacquers and resins; in the manufacture of adipic acid, benzenes, cyclohexyl chloride, nitrocyclohexane, cyclohexanol, and cyclohexanone; and in analytical chemistry for molecular weight determinations.⁽²⁾

Animal Studies

Acute

The acute toxicity of cyclohexane is extremely low;⁽³⁾ rabbits survived an 8-hour exposure at 18,500 ppm (1.85%), but 26,600 ppm was lethal after a 1-hour exposure. A concentration of 12,600 ppm resulted in lethargy,

narcosis, an increased respiration rate, and convulsions in exposed rabbits; 3330 ppm caused no visible effects.

Subchronic

In repeated exposures, Treon and associates⁽⁴⁾ found minimal microscopic changes in the liver and kidneys of rabbits exposed at 786 ppm cyclohexane for 50 periods of 6 hours each. No toxic changes were found in the tissues of rabbits after exposure for the same period at a concentration of 1.46 mg/L (434 ppm). Patty⁽⁵⁾ summarized existing information on the toxicity of cyclohexane as follows:

"A concentration of 434 ppm is believed to be safe for rabbits. Whether human beings will observe any narcotic effects or be fatigued at this concentration remains to be established. However, it seems unlikely that serious or lasting consequences will result from exposure at 300 ppm, and this should offer a satisfactory temporary bench mark until further studies are made."

Human Studies

Although Gerarde⁽⁶⁾ reports 300 ppm cyclohexane to be detectable by odor and somewhat irritating to the eyes and mucous membranes, Amoore and Hautala⁽¹⁾ state that the odor threshold is 25 ppm.

TLV Recommendation

A TLV-TWA of 300 ppm is recommended for cyclohexane, but represents a borderline of irritation. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA⁽⁷⁾ established a PEL-TWA for cyclohexane of 300 ppm. The PEL is consistent with the recommended ACGIH TLV. Cyclohexane was one of the 160 substances whose PEL was unchanged and was not evaluated during the 1989 OSHA rulemaking on air contaminants — permissible exposure limits.

NIOSH REL/IDLH: NIOSH established a REL-TWA of 300 ppm for cyclohexane by concurrence with the OSHA adopted PEL [Ex 8-47, Table N3A].⁽⁸⁾ NIOSH established an IDLH value of 10,000 ppm for this substance.

NTP Studies: NTP has conducted pharmacokinetic studies on cyclohexane but has not conducted long-term

toxicology and carcinogenesis effects studies on this substance. Cyclohexane was negative in the *Salmonella* assay.

Other Nations

Australia: 300 ppm (1990); Federal Republic of Germany: 300 ppm, short-term limit 600 ppm, 30 minutes, 4 times per shift (1990); Sweden: 300 ppm (1984); United Kingdom: 300 ppm, 10-minute STEL 375 ppm (1991).

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6. Gerarde, H.W.: *Industrial Hygiene and Toxicology*, 2nd ed., Vol. II, pp. 1208-1211. F.A. Patty, Ed. Interscience, New York (1963).
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8. National Institute for Occupational Safety and Health: Testimony of NIOSH on the Occupational Safety and Health Administration's Proposed Rule on Air Contaminants: 29 CFR Part 1910, Docket No. H-020; Table N3A (Appendix A) (August 1, 1988).

CYCLOPENTANE

CAS: 287-92-3

Pentamethylene

C₅H₁₀



TLV-TWA, 600 ppm (1720 mg/m³)

1979: TLV-TWA, 600 ppm, proposed

1979: TLV-STEL, 900 ppm, proposed

1981-present: TLV-TWA, 600 ppm

1981-1986: TLV-STEL, 900 ppm

1987: TLV-STEL, deleted

1991: Documentation revised

Chemical and Physical Properties

Cyclopentane is a flammable, mobile liquid. Chemical and physical properties include:^(1,2)

Molecular weight: 70.13

Specific gravity: 0.7460 at 20°C

Melting point: -94.4°C

Boiling point: 49.5°C

Explosive limits: upper, 8.7%; lower, 1.1% by volume in air

Flash point: -37.2°C

Solubility: insoluble in water; miscible with alcohol, ether, and other hydrocarbon solvents

Major Uses or Sources of Occupational Exposure

Cyclopentane is used chiefly as a laboratory reagent. It is found in petroleum ether and other commercial solvents that are used as a fuel, in fat and wax extraction, in paints, and in the shoe industry.⁽¹⁾ Abbritti et al.⁽³⁾ found petroleum solvents in the Italian shoe industry to contain up to 18% cyclopentane along with other pentanes, hexane, and heptane.

Background

If cyclopentane followed the metabolic route of other cyclohydrocarbons and its homolog, its systemic action and metabolite products may be less harmful than the straight chain compounds; however, it might be more irritating to the upper respiratory tract and eyes.

More recent literature adds very little information on the chronic effects of repeated and prolonged exposure to cyclopentane. This may be because it is seldom used in the neat state industrially.

Because the industrial use of pure cyclopentane is

very limited, there have been no major toxicological animal studies reported in the public literature. Therefore, this documentation rests heavily on the n-pentane animal data, literature, and documentation.

Animal Studies

Acute

Like other alicyclic hydrocarbons, cyclopentane is a central nervous system (CNS) depressant.⁽⁴⁾ Symptoms of acute exposure, in high concentrations, are excitement, loss of equilibrium, stupor, coma, and rarely, respiratory failure.

For n-pentane, 90,000–120,000 ppm caused narcosis in animals in 5–60 minutes.⁽³⁾ According to Swann et al.,⁽⁵⁾ a concentration of 130,000 ppm is fatal. Fairhall⁽⁶⁾ found only narcosis and irritation from pentane exposure. Gerarde⁽⁴⁾ summarized the literature on alkanes and alicyclics of the lower hydrocarbon liquids.

Human Studies

The National Institute for Occupational Safety and Health (NIOSH)^(7,8) criteria documents for refined petroleum solvents and for alkanes of the C₅–C₈ range added no new biological or chemical toxicological information on cyclopentane.

In 1976, Abbritti et al.⁽³⁾ studied 122 workers in the Italian shoe industry. These workers suffered polyneuropathy from glue solvents exposure. The commercial solvents contained various petroleum ethers with mixtures of C₅–C₇ hydrocarbons containing some cyclopentane (up to 18%). It is assumed that n-hexane was present in each involved solvent.

According to Oettel,⁽⁹⁾ skin exposure to commercial solvents caused a constant, painful, burning sensation and blistering of the skin after 20 minutes of confined contact. The pain subsided within 15 minutes after pentane was removed.

TLV Recommendation

Although NIOSH⁽⁷⁾ recommended a workplace exposure limit of 120 ppm for n-pentane, there seems to be no new supporting data for this lower limit or its application to recommendation of a TLV for cyclopentane. It is thought that n-hexane is usually available in these commercial solvents to account for the polyneuropathy if the airborne concentration is high and the workplace is poorly ventilated.

A TLV-TWA of 600 ppm is recommended for cyclopentane and is considered to provide a sufficient margin of safety against the risk of undue irritation and narcosis. However, in view of the report by Abbritti et al.⁽³⁾ and Gaultier et al.,⁽¹⁰⁾ the possibility that high, repeated exposures may cause polyneuropathy cannot be overlooked.

Because of the paucity of data from animal experiments or human exposure experience, and in view of n-hexane being a common component of the solvents involved in polyneuropathy, future releases of relevant information should be followed closely to substantiate the recommended TLV. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA⁽¹¹⁾ established a PEL-TWA of 600 ppm for cyclopentane. OSHA concluded that this limit would protect workers against the significant risk of irritation and narcosis that occurs at higher levels of exposure. The PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH⁽¹²⁾ has established a REL-TWA of 600 ppm for cyclopentane [Ex 8-47, Table N1] by concurrence with the OSHA PEL. NIOSH has not established an IDLH value for this substance.

NTP Studies: NTP has not conducted genetic toxicology or long-term toxicology and carcinogenesis effects studies on cyclopentane.

Other Nations

Australia: 600 ppm (1990).

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DICHLOROTETRAFLUOROETHANE

CAS: 76-14-2

CFC-114; Cryofluorane[®]; 1,2-Dichloro-1,1,2,2-tetrafluoroethane; Freon 114[®]; Genetron 114[®]; Refrigerant 114

C₂Cl₂F₄

ClF₂C-CClF₂

TLV-TWA, 1000 ppm (6900 mg/m³)

1946: MAC-TWA, 10,000 ppm

1947: MAC-TWA, 1000 ppm

1948-present: TLV-TWA, 1000 ppm

1976-1985: TLV-STEL, 1250 ppm

1986: TLV-STEL, deleted

1991: Documentation revised

Chemical and Physical Properties

Dichlorotetrafluoroethane (CFC-114) is a colorless, nearly odorless, nonflammable gas. Chemical and physical properties include:⁽¹⁻³⁾

Molecular weight: 170.93

Specific gravity: 1.5312 at 0°C (liquid)

Melting point: -94°C

Boiling point: 3.77°C

Vapor pressure: 1444 torr at 20°C

Solubility: soluble in alcohol, ether, and water at 25°C

Reactivity: reacts with chemically active metals such as sodium, potassium, calcium, powdered aluminum, zinc, and magnesium

Decomposition products: forms hydrogen chloride, phosgene, and hydrogen fluoride in contact with the above metals

Major Uses or Sources of Occupational Exposure

CFC-114 has been used primarily as an aerosol propellant, refrigerant, solvent, fire extinguisher, blowing agent, and dielectric fluid. CFC-114 is an ozone-depleting chlorofluorocarbon. The Montreal Protocol on Substances that Deplete the Ozone Layer should cause an international decline in the use and production of CFC-114 in the 1990s.⁽²⁾

Animal Studies

Acute

When inhaled, CFC-114 acts like a weak narcotic and has low toxicity.⁽²⁾ Concentrations lethal for mice, rats, and rabbits exposed for 30 minutes are in the range of 70% in air spiked to 20% oxygen.⁽⁴⁾ Two-hour exposures at 300,000-400,000 ppm disturbed the equilibrium of rats and guinea pigs.⁽⁵⁾ Nuckolls⁽⁶⁾ noted

irregular breathing but "no toxic action" in guinea pigs exposed for 2 hours at 8000-47,000 ppm. Quevauviller hours at 10,000 ppm showed no clinical effects, but microscopic examination of the lungs revealed evidence of hemorrhage. Yant et al.⁽⁸⁾ found that dogs survived 8-hour exposures at 200,000 ppm CFC-114; however, a single 16-hour exposure or three to four 8-hour exposures were lethal. High concentrations produced clinical signs of tremors, convulsions, and incoordination.

Cardiac sensitization potential of CFC-114 is considered moderate. Reinhardt and associates⁽⁹⁾ found evidence of serious arrhythmia in 1 of 12 dogs exposed at an atmosphere of 25,000 ppm CFC-114 plus intravenous epinephrine. Blood fluorocarbon concentrations of 13.8 µg/ml (arterial) and 7.2 µg/ml (venous) were reported for this level of exposure.⁽¹⁰⁾ Using a similar technique, Clark and Tinston⁽¹¹⁾ reported an effective dose (EC₅₀) of 100,000 ppm. Cardiac sensitization can be induced with endogenous epinephrine at levels of 50,000-800,000 ppm.^(9,12) Characterizing CFC-114 as intermediate among aerosol propellants in acute toxicity (based on circulatory/respiratory effects at levels > 25,000 ppm), Aviado⁽¹³⁾ generalized that CFC-114 reduced compliance and acted as a bronchoconstrictor.

Subchronic

Repeated application of CFC-114 to rabbit skin as a 40% solution in sesame oil was without effect.⁽⁵⁾ Repeated spraying with CFC-114^(14,15) produced local inflammation in rat skin and the mucous membranes of rabbit eyes, but microscopic examination showed no injury to the eyeball.

Yant and associates⁽⁸⁾ also reported that dogs survived 21 eight-hour exposures at 142,000-150,000 ppm CFC-114; the animals showed slight blood changes and symptoms ranging from incoordination to occasional convulsions. Paulet and Desbrousses⁽⁴⁾ found that a 2-week exposure of rats at 200,000 ppm, 2.5 hours/day, 5 days/week, resulted in a decreased growth rate and some pulmonary and hematologic effects; similar exposure at 100,000 ppm did not produce these effects. A 4-week study with twenty 3.5-hour exposures at 100,000 ppm⁽⁵⁾ revealed no effects in dogs, cats, guinea pigs, and rats.

Chronic/Carcinogenicity

At 10,000 ppm CFC-114, rats and rabbits exposed 2 hours/day, 5 days/week for 8 to 9 months showed no significant clinical, hematologic, or histopathologic change; also, trephined rabbits showed no significant change in electroencephalographic recordings.⁽¹⁶⁾

Genotoxicity Studies

CFC-114 gave negative results when tested in *Salmonella typhimurium* TA 15351 in the absence or

presence of a metabolic activating system.⁽²⁾

Pharmacokinetic/Metabolism Studies

Human and animal studies^(10,17,18) indicate rapid excretion of inhaled CFC-114. In a study with radiolabeled CFC-114,⁽¹⁸⁾ 30-minute retention of the dose inhaled in a single breath was 12% versus 23%, 10%, and 20% for comparable doses of trichlorofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12), and trifluorotrchloroethane (CFC-113), respectively.

Human Studies

There are limited data on exposures to CFC-114. In one study,⁽²⁾ ten subjects were exposed to CFC-11, CFC-12, and CFC-114; two mixtures of CFC-11 and CFC-12; and a mixture of CFC-12 and CFC-114 (breathing concentrations between 16 and 150 g/m³ [2300 and 21,400 ppm]) for 15, 45, or 60 seconds. Significant acute reduction of ventilatory lung capacity was reported in each case, as well as bradycardia and increased variability in heart rate and atrioventricular block. It was concluded that the mixtures exerted stronger respiratory effects than individual chlorofluorocarbons at the same level of exposure.⁽²⁾

TLV Recommendation

CFC-114 causes narcosis and asphyxia at extremely high concentrations. The cardiac sensitization potential of CFC-114 is considered moderate. A TLV-TWA of 1000 ppm is recommended to provide a wide margin of safety in preventing systemic toxicity and an adequate margin in preventing cardiac sensitization from exposure to CFC-114. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 1000 ppm for CFC-114.⁽¹⁹⁾ CFC-114 was one of the 160 substances whose PEL was unchanged and was not reevaluated during the 1989 OSHA rulemaking on air contaminants — permissible exposure limits. The PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N3A]⁽²⁰⁾ established a REL-TWA of 1000 ppm for CFC-114 by concurrence with the OSHA PEL. NIOSH has established an IDLH value of 50,000 ppm for this substance.

NTP Studies: NTP has not conducted genetic toxicol-

ogy or long-term toxicology and carcinogenesis effects studies on CFC-114.

Other Nations

Australia: 1000 ppm (1990); Federal Republic of Germany: 1000 ppm, short-term level 2000 ppm, 60 minutes, 3 times per shift (1990); United Kingdom: 1000 ppm, 10-minute STEL 1250 ppm (1991).

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ETHYL ALCOHOL

CAS: 64-17-5

Ethanol

C₂H₆O

H₃C-CH₂OH

TLV-TWA, 1000 ppm (1880 mg/m³)

1946-1947: MAC-TWA, 1000 ppm

1948-present: TLV-TWA, 1000 ppm

1991: Documentation revised

Chemical and Physical Properties

Ethyl alcohol is a colorless, flammable, volatile liquid with a vinous odor and a burning taste. An odor threshold of 84 ppm has been reported.⁽¹⁾ The stated vapor pressure permits 6.58% saturated air. Ethyl alcohol is a dangerous fire risk. Chemical and physical properties include:

Molecular weight: 46.07

Specific gravity: 0.789 at 20°C

Solidifies: < -130°C

Melting point: -114.1°C

Boiling point: 78.5°C

Vapor pressure: 43 torr at 20°C

Flash point: 12.77°C

Autoignition temperature: 422.78°C

Explosive limits: upper, 19%; lower, 3.3% by volume in air

Solubility: miscible with water and most organic solvents

Major Uses or Sources of Occupational Exposure

In suitable dilutions, ethyl alcohol is used in alcoholic beverages. It is also a solvent and is used in the manufacture of denatured alcohol and in organic synthesis.

Animal Studies

Acute

The acute toxicity of ethyl alcohol is low for both animals and humans; for rats, which are more susceptible than guinea pigs, the lethal dose by inhalation is about 13,000 ppm after 22 hours; guinea pigs, 22,000 after about 9 hours; for mice, about 29,000 ppm after 7 hours.⁽²⁾ The commonly recognized signs of overexposure are ataxia, incoordination, and drowsiness in those that survived narcosis. The narcotic dose for rats after 2 hours exposure is given as 19,260 ppm.⁽²⁾

Human Studies

Splash contact of ethyl alcohol with the eye causes

immediate stinging and burning, with reflex closure of the lids and tearing, transitory injury of the corneal epithelium, and hyperemia of the conjunctiva. A foreign body type of discomfort may be felt for a day or two, but healing is usually spontaneous and complete.⁽³⁾

Henderson and Haggard⁽⁴⁾ consider concentrations of ethyl alcohol vapor ranging from 250 to 1064 ppm safe for exposure during the working day. The vapor, even in low concentrations, is irritating to the eyes and upper respiratory tract. This feature of ethyl alcohol is more important in setting the limits for exposure than the secondary toxic effects from the absorbed alcohol.

Browning,⁽⁵⁾ in reporting on experiments on man, observed that the inhalation of 1000 ppm caused slight symptoms of poisoning and 5000 ppm caused strong stupor and morbid sleepiness. The inhalation of alcohol vapor causes local irritating effects on the eyes, headaches, sensation of heat, intraocular tension, stupor, fatigue, and a great need for sleep.

A study of the effects of inhalation of ethyl alcohol by man was carried out by Lester and Greenberg.⁽⁶⁾ Subjects exposed at 5000-10,000 ppm experienced coughing and smarting of the eyes and nose, with the symptoms disappearing within a few minutes. At 15,000 ppm, there was continuous lacrimation and coughing. Irritation of the eyes and respiratory tract were not noted at concentrations below 5000 ppm.

TLV Recommendation

Based on the lack of eye and upper respiratory tract irritation at levels below 5000 ppm⁽⁶⁾ and on widespread and long industrial hygiene experience with human exposures to ethyl alcohol, a TLV-TWA of 1000 ppm is recommended. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 1000 ppm for ethyl alcohol. The OSHA limit was established to protect workers against the significant risks of eye and upper respiratory tract irritation.⁽⁷⁾ Ethyl alcohol was one of the 160 substances whose PEL was unchanged and was not evaluated during the 1989 rulemaking on air contaminants — permissible exposure limits. The PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N3A] established a REL-TWA of 1000 ppm by concurrence with the OSHA PEL for ethyl alcohol.⁽⁸⁾ NIOSH has not

established an IDLH value for this substance.

NTP Studies: NTP has not tested ethyl alcohol in chronic toxicologic and carcinogenic studies nor in genetic toxicology studies. Studies have been completed regarding inhalation teratology and continuous breeding.

Other Nations

Australia: 1000 ppm (1990); Federal Republic of Germany: 1000 ppm, short-term level 2000 ppm, 60 minutes, 3 times per shift, Pregnancy group D, classification in one of the groups A–C is not yet possible (1990); Sweden: 1000 ppm (1989); United Kingdom: 1000 ppm (1991).

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ETHYL ETHER

CAS: 60-29-7

Diethyl ether; Diethyl oxide; Ether

C₄H₁₀O

H₃C-CH₂-O-CH₂-CH₃

TLV-TWA, 400 ppm (1210 mg/m³)

TLV-STEL, 500 ppm (1520 mg/m³)

1946-1947: MAC-TWA, 400 ppm

1948-present: TLV-TWA, 400 ppm

1976-present: TLV-STEL, 500 ppm

1991: Documentation revised

Chemical and Physical Properties

Ethyl ether is a colorless, volatile, mobile liquid with an aromatic odor and a burning, sweet taste. An odor threshold of 8.9 ppm has been reported.⁽¹⁾ Ethyl ether is extremely flammable and a severe fire and explosion hazard when exposed to heat or flame. It forms explosive peroxides unless inhibited with ferrous sulfate. Chemical and physical properties include:^(2,3)

Molecular weight: 74.12

Specific gravity: 0.7134 at 20°C

Melting point: -116.3°C

Boiling point: 34.5°C at 760 torr

Vapor density: 2.55 (air = 1.0)

Vapor pressure: 438.9 torr at 20°C

Saturated air concentration: 680,000 ppm at 25°C

Flash point: -45°C

Explosive limits: upper, 48%; lower, 1.85% by volume in air

Autoignition temperature: 180°C

Solubility: soluble in water [8.43 g/100 g at 15°C; 6.05 g/100 g at 25°C (hygroscopic)]; miscible with the lower aliphatic alcohols, benzene, chloroform, petroleum ether, other fat solvents, and many oils

Major Uses or Sources of Occupational Exposure

Ethyl ether is used as a solvent for waxes, fats, oils, perfumes, alkaloids, and gums. It is also an important reagent in organic syntheses, especially in Grignard- and Wurtz-type reactions.⁽²⁾

Human Studies

The primary physiologic effect of ethyl ether is narcosis and general anesthesia. Concentrations of ethyl ether ranging from 100,000 to 150,000 ppm are required for induction of anesthesia; however, exposure at this concentration may produce fatalities due to respiratory arrest. Maintenance of anesthesia is achieved at approximately 50,000 ppm and the lowest anesthetic limit

is 19,000 ppm.⁽³⁾ Ethyl ether used for anesthesia has produced abnormal liver function in patients.

Repeated exposures of workers in industry were often intentional ether jags.⁽³⁾ Symptoms resulting from chronic exposure consist of loss of appetite, exhaustion, headache, sleepiness, dizziness, excitation, and psychic disturbances.⁽⁴⁾ Albuminuria and polycythemia may result.⁽³⁾ A degree of tolerance may be acquired through repeated exposure.⁽⁴⁾

On the skin, ethyl ether has no deleterious effect provided contact is of short duration; repeated exposure causes drying and cracking due to extraction of oils. Irritation to the mucous membranes and eyes does occur from exposure either to the liquid or to high concentrations of the vapor.⁽³⁾

Nelson et al.⁽⁵⁾ reported that complaints of nasal irritation of volunteer subjects began at 200 ppm ethyl ether and that a concentration of 300 ppm was considered objectionable as a working atmosphere. Henderson and Haggard⁽⁶⁾ estimated that, at a concentration of 400 ppm of ethyl ether, a human of average weight would absorb a maximum of 1.25 g and the concentration in the blood would be 0.018 g/L. This concentration in the blood is not associated with any signs of intoxication. Also, the inhalation of 2000 ppm, if continued to equilibrium, would result in the absorption of some 6.25 g of ether and a concentration of 0.09 g/L of blood, which would cause dizziness in some persons. Amor⁽⁷⁾ stated that unsatisfactory exposure conditions would exist only if the air concentration is more than 500 ppm.

Cook⁽⁸⁾ stated that industrial exposures at 500 to 1000 ppm ethyl ether or more did not result in demonstrable injury to health, but a limit of 500 ppm seemed justifiable to avoid irritation and complaint.

TLV Recommendation

Ethyl ether has predominantly narcotic properties leading to anesthesia; it is also an eye and respiratory irritant. In view of data presented above,^(7,8) and the fact that persons exposed experimentally did not have the opportunity to develop the tolerance which has been observed in workers, a TLV-TWA of 400 ppm and a STEL of 500 ppm are recommended. These concentrations should minimize the potential for demonstrable injury to health, irritation, or signs of narcosis among exposed workers.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 400 ppm and a STEL of 500 ppm for ethyl ether. OSHA concluded that these limits were necessary to protect exposed workers against the significant risk of narcosis and irritation.⁽⁹⁾ The PELs are consistent with the recommended TLV.

NIOSH REL/IDLH: NIOSH has not established a

REL for ethyl ether. NIOSH [Ex 8-47, Table N2]⁽⁹⁾ did not concur with OSHA's proposed limits and noted that some individuals may experience sensory irritation upon exposure to these limits as evidenced by the report of Nelson et al.⁽⁵⁾ OSHA noted that this finding was not supported by Amor.⁽⁷⁾ NIOSH has established an IDLH value of 19,000 ppm for this substance. The IDLH was based upon the lower explosive limit [LEL].

ACGIH Rationale for TLVs that Differ from the PEL or REL: The TLV for ethyl ether is based on the statements by both Amor and Cook that irritation and unsatisfactory conditions would be avoided at air concentrations of 500 ppm. The TWA was set at a level that would not be associated with any signs of intoxication.

NTP Studies: NTP has not conducted long-term toxicology and carcinogenesis effects studies on ethyl ether. The substance is on test in the *Salmonella* assay.

Other Nations

Australia: 400 ppm, STEL 500 ppm (1990); Federal Republic of Germany: 400 ppm, short-term level 800 ppm, 30 minutes, 4 times per shift, Pregnancy group D, data insufficient for a final evaluation (1990); Sweden: 400 ppm, short-term value 500 ppm, 15 minutes (1989); United Kingdom: 400 ppm, 10-minute STEL 500 ppm (1991).

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HEPTANE (n-Heptane)

CAS: 142-82-5

C₇H₁₆

H₃C-C₅H₁₀-CH₃

TLV-TWA, 400 ppm (1640 mg/m³)

TLV-STEL, 500 ppm (2050 mg/m³)

1946-1947: MAC-TWA, 500 ppm

1948-1975: TLV-TWA, 500 ppm

1974: TLV-TWA, 400 ppm, proposed

1976-present: TLV-TWA, 400 ppm; TLV-STEL, 500 ppm

1992: Documentation revised

Chemical and Physical Properties

Heptane is a volatile, flammable liquid, with nine isomers. Among the isomers are n-heptane, isoheptane (2-methyl-hexane), neoheptane (2,2-dimethylpentane), triptane (2,2,3-trimethylbutane), 2,3- and 2,4-dimethylpentane, and 3-methylhexane. An odor threshold of 150 ppm has been reported for heptane.⁽¹⁾ Chemical and physical properties include:⁽²⁾

Molecular weight: 100.20

Specific gravity: 0.673-0.698

Melting point: -90.7°C (n-heptane)

Boiling point: 98.4°C (n-heptane); 90°C (isoheptane)

Vapor pressure: 47.7 torr at 25°C (n-heptane)

Flash points: -4.4°C (n-heptane); -27.8°C (isoheptane); -28.9°C (2,3- and 2,4-dimethylpentane), closed cup

Solubility: insoluble in water; miscible with nonpolar solvents; soluble, but not completely miscible, with solvents such as alcohols (all isomers)

Major Uses or Sources of Occupational Exposure

n-Heptane is a standard for octane rating measurements; triptane is used in aviation fuel. All isomers are employed in organic synthesis and are ingredients of gasoline and rubber solvent naphtha and other petroleum solvents that are used as fuels and solvents.

Animal Studies

Acute

Fuhner⁽³⁾ reported that, in concentrations of 10,000 to 15,000 ppm, heptane produced narcosis in mice within 30 to 50 minutes. Exposure at higher concentrations (15,000 to 20,000 ppm) for 30 to 60 minutes caused convulsions and death in mice; inhalation of 48,000 ppm caused respiratory arrest in three of four head-exposed mice within 3 minutes.⁽⁴⁾

Human Studies

Patty and Yant⁽⁵⁾ reported that inhalation of 1000 ppm heptane for 6 minutes was associated with a slight dizziness; inhalation of higher concentrations for shorter periods resulted in marked vertigo, incoordination, and hilarity. Signs of central nervous system (CNS) involvement occurred in the absence of noticeable mucous membrane irritation and were noticed promptly on entering such atmospheres. Brief exposures (4 minutes) to high levels (5000 ppm) produced complaints of nausea, loss of appetite, and a "gasoline-like" taste that persisted for several hours after cessation of exposure. Flury and Zernik⁽⁶⁾ reported the fatal concentration as 16,000 ppm. A summary of published effects of heptane and other paraffinic hydrocarbons was published by Sandmeyer.⁽²⁾

Although chronic adverse effects on the nervous system have not been attributed to heptane itself, Cavigneaux⁽⁷⁾ stated that numerous cases of polyneuritis have been reported following prolonged exposure to a petroleum fraction with a boiling range of between 70°C and 100°C. Such a fraction would normally contain various isomers of heptane as major ingredients.

The National Institute for Occupational Safety and Health (NIOSH)⁽⁸⁾ cited a paper by Truhaut et al.⁽⁹⁾ in which similar signs of neurologic disorders were found in rats exposed to technical heptane as were found in a group of workers exposed to hexane. A report⁽¹⁰⁾ of polyneuropathy among workers exposed to a solvent containing 80% pentane, 14% heptane, and 5% hexane is also mentioned, with the authors' conclusion⁽¹⁰⁾ that pentane and heptane, as well as n-hexane, might be neurotoxic. A similar conclusion by Cavigneaux has already been noted.⁽⁷⁾ This opinion ignores the work of DiVincenzo et al.⁽¹¹⁾ and others who conclude that the neurotoxic properties associated with exposure to n-hexane or methyl butyl ketone (see the respective TLV Documentations) are due to their metabolism to the same neurotoxic compounds.

Since the heptanes are major ingredients of rubber solvent, additional information on their toxicity may be inferred from the data in the documentation for that petroleum fraction (see TLV Documentation for Rubber solvent [Naphtha]).

TLV Recommendation

All of the readily measurable effects, such as narcosis and respiratory irritation, indicate heptane to be much more acutely toxic in these respects than n-hexane, and no reports of delayed neurotoxicity in humans or animals have come to the attention of the TLV Committee.

The TLV Committee believes that the preponderance of available evidence indicates that n-hexane is unique among the alkanes in its neurotoxicity. The TLV for heptane, therefore, is based on its narcotic and irritative effects, which are greater than those of pentane or

n-hexane, and less than those of octane. Accordingly, a TLV-TWA of 400 ppm and a STEL of 500 ppm are recommended for all isomers of heptane.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 400 ppm and a STEL of 500 ppm for heptane. OSHA concluded that the TWA and STEL together would substantially reduce the significant risk of narcosis.⁽¹²⁾ The OSHA PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH established a REL-TWA of 85 ppm and a 15-minute ceiling of 440 ppm for heptane.⁽⁸⁾ NIOSH [Ex 8-47, Table N2] did not concur with the OSHA PEL for heptane.⁽¹²⁾ NIOSH established an IDLH value of 5000 ppm for heptane.

ACGIH Rationale for TLVs that Differ from the PEL or REL: NIOSH recommended on a mg/m³ basis the same occupational exposure limits for each of the C₅-C₈ alkanes. These recommended exposure limits were based on NIOSH's position that there was insufficient evidence to ascribe the peripheral neuropathy noted following exposure to alkanes as being due solely to exposure to hexane and its metabolites. Conversely, ACGIH and OSHA believe that the preponderance of available evidence indicates that n-hexane is unique among the alkanes in its toxicity. Thus, the TLV for heptane is based primarily on its narcotic and irritative effects.

NTP Studies: NTP has not conducted genetic toxicology or long-term toxicology and carcinogenesis effects studies on heptane.

Other Nations

Australia: 400 ppm, STEL 500 ppm (1990); Federal Republic of Germany: 500 ppm, 1000 ppm, 30 minutes, 4 times per shift (1991); Sweden: 300 ppm, short-term value 375 ppm, 15 minutes (1989); United Kingdom: 400

ppm, 10-minute STEL 500 ppm (1991).

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HEXANE ISOMERS, OTHER THAN n-HEXANE

C₆H₁₄

C₃H₇CH(CH₃)₂ [isohexane];
CH₃)₂CHCH(CH₃)₂ [2,3-dimethylbutane];
C₂H₅C(CH₃)₃ [neohexane]

TLV-TWA, 500 ppm (1760 mg/m³)

TLV-STEL, 1000 ppm (3500 mg/m³)

1980: TLV-TWA, 500 ppm; TLV-STEL, 1000 ppm, proposed

1982-present: TLV-TWA, 500 ppm; TLV-STEL, 1000 ppm

1992: Documentation revised

Chemical and Physical Properties

The hexanes are clear, highly volatile liquids with a mild gasoline-like odor. The isomers include: isohexane (2-methylpentane), 3-methylpentane, neohexane (2,2-dimethylbutane), and 2,3-dimethylbutane. Chemical and physical properties include:⁽¹⁾

Molecular weight: 86.17

Boiling point: 50°–68°C

Flash points: –47.78°C (neohexane); –23.33°C (isohexane); closed cup

Solubility: insoluble in water; soluble in ether; readily soluble in alcohol

Major Uses or Sources of Occupational Exposure

Commercial hexanes are solvents for vegetable oils, glues, coatings, and paints. They are also found in gasoline and are used as intermediates for chemicals and as constituents of rubber solvent and petroleum ether.

Animal Studies

Little information is available on individual isomers of hexane. The following information was reported for hexane mixtures of undetermined purity. Hexane is three times as toxic to mice as is pentane; narcosis was produced in mice within 30 to 60 minutes at concentrations of 30,000 ppm, and concentrations from 35,000 to 40,000 ppm resulted in convulsions and death.^(2,3)

Human Studies

In humans, exposure to hexane for 10 minutes at 2000 ppm resulted in no effects, but 5000 ppm caused dizziness and a sense of giddiness.⁽⁴⁾ At concentrations of 1400 to 1500 ppm, Drinker et al.⁽⁵⁾ found slight nausea, headache, and eye and throat irritation. Nelson and co-workers⁽⁶⁾ found no irritation at 500 ppm in unacclimated subjects. When concentrations exceeded 1000 ppm, signs of central nervous system (CNS) depression, such as dizziness, have been frequently observed, but

they were not observed from levels below 500 ppm.⁽⁷⁾

Sandmeyer⁽¹⁾ stated that after exposure to high concentrations of hexane isomers, mucous membrane irritation would be expected. Hexane isomers were predicted to have a low acute oral toxicity and perhaps to be absorbed through the skin. Isohexane is predicted to have narcotic properties and is a documented cardiac sensitizer; however, based on comparative structure–metabolism relationships, it is not expected to induce neurotoxicity.⁽¹⁾

TLV Recommendation

It is the opinion of the TLV Committee that the metabolites of n-hexane (primarily 5-hydroxy-2-hexanone and 2,5-hexanedione) are responsible for its neurotoxicity. This conclusion is supported by the similar production of these metabolites after exposure to methyl n-butyl ketone, a compound which can induce an identical syndrome. Based on known patterns of hepatic microsomal oxidation and marked variations in structures of the hexane isomers considered here, it is considered unlikely that all hexanes would follow the same metabolic route in the body.

A TLV-TWA of 500 ppm is recommended for isomers of hexane and mixtures of hexanes containing no n-hexane, based on the above metabolic data and the absence of adverse effects from exposure to concentrations at or below 500 ppm. It is further recommended that the n-hexane TLV (50 ppm TWA) would apply not only to n-hexane itself but also to commercial hexane which contained greater than 5% n-hexane.

A STEL of 1000 ppm is recommended in order to prevent objective depression of the CNS. For hexane isomers containing less than 5% n-hexane, a TLV-TWA of 500 ppm should provide adequate protection from the nausea, headache, ocular and upper respiratory tract irritation, and CNS depression associated with hexane inhalation in the absence of additional organic compounds with narcotic or neurotoxic characteristics. No data are available upon which to base a determination of the potential for percutaneous absorption.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 500 ppm and a STEL of 1000 ppm for hexane isomers other than n-hexane. OSHA concluded that these limits would protect workers against the significant risk of experiencing narcosis and of developing neuropathy.⁽⁸⁾ The PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH established a REL-TWA for the hexane isomers of 100 ppm and a 15-minute ceiling of 510 ppm.⁽⁹⁾ NIOSH [Ex 8-47, Table N2] did not concur with the OSHA PEL.⁽⁸⁾ NIOSH has not established an IDLH value for the hexane isomers.

ACGIH Rationale for TLVs that Differ from the PEL

or REL: NIOSH⁽⁹⁾ in its criteria document concluded that all of the C₅-C₈ alkanes are potential neuropathic agents and should have the same PELs as those established at that time for n-hexane. ACGIH and OSHA believe it is inconsistent to base exposure limits for the isomers of hexane on their unproven neurotoxicity. These agencies consider it unlikely that all the hexanes would follow the same metabolic route in the body, in view of the known patterns of xenobiotic biotransformation in animals and humans identified with the marked variations in structure of the various hexane molecules.

NTP Studies: NTP has not conducted genetic toxicology or long-term toxicology and carcinogenesis effects studies on the isomers of hexane other than n-hexane.

Other Nations

Australia: 500 ppm, STEL 1000 ppm (substance under review) (1990); Federal Republic of Germany: 50 ppm, short-term level 100 ppm, 4 times per shift, Group C pregnancy, no reason to fear risk of damage to embryo or fetus when MAK and BAT values are adhered to (1991); Sweden: 300 ppm, short-term value 375 ppm, 15 minutes (1989); United Kingdom: 500 ppm, 10-minute STEL 1000 ppm (1991).

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ISOPROPYL ALCOHOL

CAS: 67-63-0

Isopropanol; 2-Propanol

C₃H₈O

(H₃C)₂CHOH

TLV-TWA, 400 ppm (983 mg/m³)

TLV-STEL, 500 ppm (1230 mg/m³)

1966-present: TLV-TWA, 400 ppm

1974-1980: Skin notation

1976-present: TLV-STEL, 500 ppm

1981: Skin notation, deleted

1992: Documentation revised

Chemical and Physical Properties

Isopropyl alcohol is a colorless, flammable liquid with a slight odor resembling rubbing alcohol. An odor threshold of 22 ppm has been reported.⁽¹⁾ Chemical and physical properties include:⁽²⁻⁴⁾

Molecular weight: 60.09

Specific gravity: 0.7861 at 20°C

Freezing point: -89.5°C

Boiling point: 82.4°C at 760 torr

Vapor pressure: 33 torr at 20°C

Flash points: 11.7°C, closed cup; 18.3°C, open cup

Explosive limits: upper, 12.7%; lower, 2.3% by volume in air

Autoignition temperature: 399°C

Solubility: miscible with water, ethyl alcohol, and ethyl ether

Major Uses or Sources of Occupational Exposure

Isopropyl alcohol is a raw material for the synthesis of acetone, glycerin, and other chemicals. Its physical properties are similar to those of ethyl alcohol, and it is employed as a solvent for comparable purposes, for oils, gums, and resins and as a deicing agent for liquid fuels. A 70% solution of isopropyl alcohol in water is widely used as rubbing alcohol. It is also found in skin lotions, hair care and shaving products, and certain home aerosols. Isopropyl alcohol is made by reacting propylene with sulfuric acid and hydrolysis of the reaction product.⁽⁵⁻⁷⁾

Animal Studies

Acute

The acute depressant dose for the animal central nervous system (CNS) is approximately one-half that of ethanol.⁽⁸⁻¹⁰⁾ Smyth⁽¹¹⁾ found that rats survived 4 hours of exposure to isopropyl alcohol vapor at 12,000 ppm, but that a similar exposure for 8 hours killed half of the

exposed animals. Mice exposed at 3250 ppm for 460 minutes developed ataxia, prostration, and finally, narcosis.⁽¹²⁾ Guinea pigs exposed at 400 ppm for 24 successive hours had slight changes in the mucosa of the nose and trachea, whereas exposure at 5500 ppm for the same duration caused severe pathological degeneration of the respiratory mucosa.⁽¹³⁾

In the eyes of a rabbit, 0.1 ml of 70% isopropyl alcohol caused conjunctivitis, iritis, and corneal opacity.⁽²⁾

Subchronic

Symptomatology evidence indicates that a slight tolerance is acquired to the narcotic effects of isopropyl alcohol.⁽²⁾ Lehman et al.⁽¹⁴⁾ reported that three dogs acquired a tolerance within 7 months to 4% isopropyl alcohol given in drinking water. This tolerance was manifested by a greater coordination at a given isopropyl alcohol blood level and by an increased rate of removal of the alcohol from the blood.

Chronic/Carcinogenicity

Weil et al.⁽¹⁵⁾ conducted studies in which mice inhaled isopropyl alcohol vapor 5 days/week, 3 to 7 hours/day for 5 to 8 months at 3000 ppm. Isopropyl oils from two manufacturing processes were similarly evaluated for carcinogenic potential. Isopropyl alcohol showed no significant tumorigenic activity, whereas increased tumor incidence was found in mice exposed to one of the oils. Weil et al.⁽¹⁵⁾ also evaluated isopropyl alcohol and isopropyl oil in mice via subcutaneous injection of 0.025 ml of undiluted substance once weekly for 20 to 40 weeks. The International Agency for Research on Cancer (IARC) determined that the evidence for the carcinogenicity of isopropyl alcohols and isopropyl oils to animals was inadequate.⁽¹⁶⁾

Pharmacokinetic/Metabolism Studies

Because of the slow metabolism and ketosis associated with isopropanol intoxication, the duration of CNS depression (to frank coma) is longer than that seen after ethanol. Isopropanol is metabolized far more slowly in humans than is ethanol and the major metabolite is acetone. It is thought that isopropanol metabolism proceeds via the action of alcohol dehydrogenase; however, the elimination kinetics do not resemble those for either ethanol or methanol.^(9,17-20)

Dermal absorption has been considered toxicologically insignificant.⁽²¹⁾ The cases of deep coma associated with skin contact⁽²²⁻²⁴⁾ are thought to be a consequence of gross isopropanol vapor inhalation in rooms with inadequate ventilation, rather than being attributable to percutaneous absorption of isopropanol per se.⁽²⁵⁾

Human Studies

The probable oral lethal dose in humans is 240 ml,

but ingestion of only 20 ml has caused poisoning.⁽²⁵⁾

In common with other alcohols, isopropyl alcohol has moderate narcotic properties. Nelson and co-workers⁽²⁶⁾ found that 400 ppm caused mild irritation of the eyes, nose, and throat; at 800 ppm, the symptoms were intensified although not severe; most subjects found this concentration objectionable. Fairhall⁽²⁷⁾ considered isopropyl alcohol to be similar in action to ethyl alcohol but about twice as toxic.

In the manufacture of isopropyl alcohol, an excess of paranasal sinus cancers was found among workers engaged in the process. These were attributed to isopropyl oil, a waste product in the operation. Use of a more dilute sulfuric acid, at a higher temperature, is said to have eliminated the cancer hazard from this process.⁽²⁸⁾ There is no credible evidence that exposure to isopropyl alcohol itself represents a carcinogenic threat.⁽¹⁶⁾

A criteria document by the National Institute for Occupational Safety and Health (NIOSH), published in 1976, contains an extensive review of the toxicology of isopropyl alcohol.⁽²⁾ No new data on occupational effects are presented. Most of the cases of human intoxication were in alcoholics who drank rubbing alcohol containing isopropyl alcohol. Chronic alcoholics are more tolerant of systemic isopropyl alcohol than are persons who do not consume ethanol;⁽²⁹⁾ alcoholics have survived ingestion of as much as 1 pint of 70% isopropanol.⁽³⁰⁾

TLV Recommendation

Isopropyl alcohol is of low toxicity by any route, and the TLV is set on the basis of eye, nose, and throat irritation. Accordingly, a TLV-TWA of 400 ppm and a STEL of 500 ppm are recommended for isopropyl alcohol. These concentrations should minimize the potential for inducing objective narcotic effects or significant irritation of the eyes or upper respiratory tract. Although data are lacking, it is not believed that chronic effects would result from exposures at or below the TLV. This limit is intermediate between the TLVs for ethyl and n-propyl alcohols, which are less and more toxic than isopropyl alcohol, respectively.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 400 ppm and a STEL of 500 ppm for isopropyl alcohol. OSHA concluded that these dual exposure limits were necessary to protect workers from the significant risks of narcosis and eye and mucous membrane irritation associated with chronic and acute exposure to isopropyl alcohol.⁽³¹⁾ The OSHA PELs are consistent with the recommended ACGIH TLVs.

NIOSH REL/IDLH: In its criteria document, NIOSH established a REL-TWA of 400 ppm for isopropyl alcohol.⁽²⁾ NIOSH [Ex 8-47, Table N1] established a STEL of 500 ppm for isopropyl alcohol by concurrence with the

OSHA PEL.⁽³¹⁾ NIOSH established an IDLH value of 12,000 ppm for this substance.

NTP Studies: NTP has not conducted long-term toxicology and carcinogenesis effects studies on isopropyl alcohol. NTP has completed an inhalation teratology study on this substance. Isopropyl alcohol was negative in the *Salmonella* assay.

Carcinogenic Classification

IARC: Group 3, not classifiable as to its carcinogenicity to humans.

Other Nations

Australia: 400 ppm, STEL 500 ppm, (1990); Federal Republic of Germany: 400 ppm, short-term level 800 ppm, 30 minutes, 4 times per shift, Pregnancy group D classification is not yet possible (1991); Sweden: 150 ppm, short-term value 250 ppm, 15 minutes (1989); United Kingdom: 400 ppm, 10-minute STEL 500 ppm (1991).

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NONANE

CAS: 111-84-2 (n-Nonane)

n-Nonane; 2,2,5-Trimethylhexane

C₉H₂₀

H₃C-(CH₂)₇-CH₃ [n-Nonane]

(H₃C)₃-C-(CH₂)₂-CH-(CH₃)₂ [2,2,5-Trimethylhexane]

TLV-TWA, 200 ppm (1050 mg/m³)

1974: TLV-TWA, 200 ppm; proposed

1976-present: TLV-TWA, 200 ppm

1976-1986: TLV-STEL, 250 ppm

1987: TLV-STEL deleted

1992: Documentation revised

Chemical and Physical Properties

Nonane is a colorless liquid having an odor similar to that of gasoline. An odor threshold of 47 ppm has been reported.⁽¹⁾ Chemical and physical properties of include:^(2,3)

Molecular weight: 128.26

Specific gravity: 0.7176 at 20°C

Freezing point: -53.5°C

Boiling point: 150.8°C

Vapor pressure: 10 torr at 38°C

Flash point: 31°C, closed cup

Explosive limits: upper, 2.9%; lower, 0.87% by volume in air

Solubility: insoluble in water; very soluble in alcohol and ether; infinitely soluble in acetone and benzene

Major Uses or Sources of Occupational Exposure

Nonane is used in organic synthesis, as a distillation chaser, and in biodegradable detergents. Nonanes are major ingredients of such petroleum fractions as VM & P naphtha, 140 flash and Stoddard solvents, and gasoline.

Animal Studies

Acute

The 4-hour LC₅₀ for rats of 3200 ppm has been found for n-nonane,⁽⁴⁾ or about the same as the 3400 ppm of VM&P naphtha.⁽⁵⁾ The LC₅₀ for nonane published by Carpenter et al.⁽⁴⁾ is markedly lower than the lethal concentrations for mice reported by earlier investigators for octane (13,500 ppm) or heptane (16,000 ppm)⁽⁶⁾ for exposures of 30 to 60 minutes. The latter values are comparable to the concentrations found by Swann et al.⁽⁷⁾ to cause death of mice in respiratory arrest after inhalation of octane (16,000 ppm) or hexane (48,000 ppm) for

3 to 5 minutes.

Subchronic

A 65-day (6 hours/day, 5 days/week) no-observed-adverse-effect level (NOAEL) of 590 ppm of n-nonane was found for rats.⁽⁴⁾ The n-nonane subchronic inhalation NOAEL was comparable with the 560 ppm inhalation NOAEL for VM & P naphtha.⁽⁵⁾

Chronic

The National Research Council⁽⁸⁾ listed nonane along with 31 other organic compounds as priority environmental contaminants for which no chronic toxicity data exist.

TLV Recommendation

There are only very limited data upon which to base a TLV for nonane. The primary toxicologic effect associated with inhalation of high concentrations of the aliphatic hydrocarbons is depression of the central nervous system, leading to coma with inhibition of deep tendon reflexes.⁽⁶⁾ The acute toxicities of the alkanes and their narcotic potentials increase with an increase in carbon chain length.⁽⁹⁾ Nonane, by analogy with the properties of heptane and octane, is expected to defat the skin, to cause chemical dermatitis or, with prolonged contact, necrosis.⁽²⁾ Aspiration into the lung after ingestion or during eructation or vomiting is expected to cause chemical pneumonitis; this results in an acute fulminating hemorrhagic and usually fatal bronchopneumonia. Death occurs as a result of the severe pulmonary edema.⁽¹⁰⁾ Accordingly, a TLV-TWA of 200 ppm for nonane (all isomers) in workplace air is recommended by comparison with that for octane (TLV-TWA of 300 ppm). At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 200 ppm for nonane. OSHA concluded that this limit would protect workers against the significant risk of narcosis associated with exposure to nonane at levels above the PEL.⁽¹¹⁾ The OSHA PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N1] established a REL-TWA of 200 ppm by concurrence with the OSHA PEL for nonane.⁽¹¹⁾ NIOSH has not established an IDLH value for this substance.

NTP Studies: Nonane was negative in the *Salmonella* assay. NTP has not conducted other genetic toxicology, other short-term toxicology, or long-term toxicology and carcinogenesis effects studies of nonane.

Other Nations

Australia: 200 ppm (1990); Sweden: 150 ppm, short-term value 200 ppm, 15 minutes (1989).

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OCTANE

CAS: 111-65-9 (n-Octane)

n-Octane; Isooctane

C₈H₁₈

H₃C-C₆H₁₂-CH₃ (all isomers)

TLV-TWA, 300 ppm (1400 mg/m³)

TLV-STEL, 375 ppm (1750 mg/m³)

1946-1947: MAC-TWA, 500 ppm

1948-1969: TLV-TWA, 500 ppm

1968: TLV-TWA, 400 ppm, proposed

1970-1975: TLV-TWA, 400 ppm

1974: TLV-TWA, 300 ppm, proposed

1976-present: TLV-TWA, 300 ppm; TLV-STEL, 375 ppm

1992: Documentation revised

Chemical and Physical Properties

The isomers of octane are colorless, flammable liquids. There are 18 isomers, including n-octane and isooctane (2,2,4-trimethylpentane). Odor thresholds of 48 ppm⁽¹⁾ and 150 ppm⁽²⁾ have been reported. Chemical and physical properties of n-octane and isooctane include:^(3,4)

Molecular weight: 114.22

Specific gravity at 20°C: 0.7025 (n-octane); 0.6919 (isooctane)

Melting point: -56.8°C (n-octane); -116°C (isooctane)

Boiling point: 125.7°C (n-octane); 99.2°C (isooctane)

Flash points: 13°C (n-octane), -12°C (isooctane), closed cup; 22°C (n-octane), open cup

Explosive limits: upper, 4.66%; lower, 0.96% by volume in air (n-octane); upper, 6%; lower, 1.1% by volume in air (isooctane)

Vapor pressure: 10.0 torr at 19°C (n-octane); 40.6 torr at 21°C (isooctane)

Solubility: insoluble in water; slightly soluble in ethyl alcohol; and soluble in ethyl ether and benzene (n-octane and isooctane)

The other 16 isomers of octane are of intermediate volatility between those of n-octane and isooctane.

Major Uses or Sources of Occupational Exposure

n-Octane is used as a solvent, in organic synthesis, and in azeotropic distillations. Isooctane is a standard additive for combustion control properties of gasoline (octane number). The octanes are present in gasoline and petroleum solvents such as VM&P naphtha.

Animal Studies

Sandmeyer⁽⁵⁾ has summarized the available toxicologic information on octane and other paraffins in

which narcosis and mucous membrane irritation are noted as common properties that progress in intensity with increasing molecular weight.

Acute

Narcosis was produced in mice in 30 to 90 minutes when exposed at 6600 to 13,700 ppm octane in air.⁽⁵⁾ Respiratory arrest occurred in one of four mice within 5 minutes at 16,000 ppm and in four of four mice within 3 minutes when exposed at 32,000 ppm.⁽⁶⁾

Swann et al.⁽⁶⁾ found the response of mice to high concentrations of isooctane to be different from that of normal heptane, hexane, and pentane. Irritation and respiratory arrest occurred at lower concentrations, but there was no apparent anesthesia.

Human Studies

Patty and Yant⁽⁷⁾ stated that the narcotic concentration of octane to humans was 10,000 ppm, while Flury and Zernik⁽⁸⁾ estimated the narcotic concentration at 8000 ppm and the fatal concentration at 13,500 ppm. From these data, it can be inferred that octane is 1.2 to 2 times more potent as a narcotic than heptane (see the TLV Documentation for heptane).

TLV Recommendation

There are only very limited data from which to draw rigorous support for the octane TLV. Octane is a mucous membrane irritant in animals, and it has caused narcosis at high concentrations.

On the basis of the comparison of the acute response of humans and animals to inhaled octane isomers and by analogy with other paraffinic hydrocarbons, a TLV-TWA of 300 ppm and a STEL of 375 ppm are recommended. A TLV-TWA of 300 ppm is somewhat higher than would result from a directly proportional relationship between the acute narcotic effects of octane and the lower members of the series.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 300 ppm and a STEL of 375 ppm for octane. OSHA concluded that these limits would protect workers from the significant risk of narcosis associated with exposure levels greater than the PEL.⁽⁹⁾ The OSHA PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH established a REL-TWA for octane of 75 ppm and a ceiling concentration of 385 ppm determined over a 15-minute sampling period.⁽¹⁰⁾ NIOSH established an IDLH value of 5000 ppm for this substance. NIOSH [Ex 8-47, Table N2] did not concur with the OSHA PEL for octane on the basis that all C₅-C₈ alkanes present a neurotoxic hazard similar to that of n-hexane and that adoption of the RELs would afford

more protection from the development of polyneuropathy.⁽¹¹⁾

ACGIH Rationale for TLVs that Differ from the PEL or REL: Both ACGIH and OSHA disagree with the conclusions that form the basis of the NIOSH RELs for the alkane series C₅-C₈. ACGIH has cited published data which show that the polyneuropathy induced by exposure to n-hexane is unique due to the products of its *in vivo* biotransformation. (See the TLV Documentations for n-hexane and 2-butanone.) Other structurally related alkanes do not share the same metabolic fate.⁽¹²⁾ The NIOSH REL appears to be based on the belief that the polyneuropathy induced by chronic exposure to n-hexane is a general effect of exposure to paraffin hydrocarbons. The NIOSH REL rationale appears to reject the well-established basis for the neurotoxicity of n-hexane which is due to the action of its metabolites, which are the same as those of methyl n-butyl ketone (2-butanone).⁽¹²⁾ The NIOSH rationale also assumes that the chronic effects on the nervous system do not parallel the acute effects, which are several times greater for octane than for hexane.

NTP Studies: NTP has not conducted genetic toxicology, other short-term toxicology, or long-term toxicology and carcinogenesis bioassays with any of the octane isomers.

Other Nations

Australia: 300 ppm, STEL 375 ppm (1990); Federal Republic of Germany: 500 ppm, short-term level 1000 ppm, 30 minutes, 4 times per shift (1991); Sweden: 200 ppm, short-term level 300 ppm, 15 minutes (1990); United Kingdom: 300 ppm, 10-minute STEL 375 ppm (1991).

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PENTANE

CAS: 109-66-0 (n-Pentane)

Amyl hydride

C₅H₁₂

H₃CCH₂CH₂CH₂CH₃ (n-Pentane)

(H₃C)₂CHCH₂CH₃ (Isopentane)

C(CH₃)₄ (Neopentane)

TLV-TWA, 600 ppm (1770 mg/m³)

TLV-STEL 750 ppm (2210 mg/m³)

1946: MAC-TWA, 5000 ppm

1947: MAC-TWA, 1000 ppm

1948-1969: TLV-TWA, 1000 ppm

1968: TLV-TWA, 500 ppm, proposed

1970-1975: TLV-TWA, 500 ppm

1974: TLV-TWA, 600 ppm, proposed

1976-present: TLV-TWA, 600 ppm; TLV-STEL, 750 ppm.

1992: Documentation revised

Chemical and Physical Properties

Pentane is a colorless, flammable liquid with a gasoline-like odor. It exists in three isomeric forms: n-pentane, the most important isomer, followed by the more volatile isopentane, and then neopentane. Neopentane forms tetragonal crystals upon solidification. An odor threshold of 400 ppm has been reported.⁽¹⁾ Chemical and physical properties of the isomers include:⁽²⁾

Molecular weight: 72.15

Specific gravity at 20°C: 0.6262 (n-pentane); 0.6197 (isopentane); 0.5910 (neopentane)

Melting point: -129.7°C (n-pentane); -159.9°C (isopentane); -16.6°C (neopentane)

Boiling point: 36.1°C (n-pentane); 27.8°C (isopentane); 9.5°C (neopentane)

Vapor pressure: 400 torr at 18.5°C (n-pentane); 595 torr at 21.1°C (isopentane); 1100 torr at 21.8°C (neopentane)

Flash point: -49°C (n-pentane), -51°C (isopentane), -6.67°C (neopentane), closed cup

Explosive limits: upper, 7.8%; lower, 1.4% by volume in air

Solubility: insoluble in water (isopentane and neopentane); slightly soluble in water (n-pentane); soluble in ethanol (neopentane) and ethyl ether (neopentane); very soluble in ethyl ether (n-pentane and isopentane) and in ethanol (n-pentane and isopentane)

Major Uses or Sources of Occupational Exposure

Pentane is present in volatile petroleum fractions,

some of which are used as solvents. The pure compound is employed in the manufacture of ice, low-temperature thermometers, as a blowing agent for plastics, and in solvent extraction processes. Isopentane is also used as a blowing agent, and neopentane is employed in the manufacture of butyl rubber.

Animal Studies

Acute

Sandmeyer⁽²⁾ and von Oettingen⁽³⁾ summarized available toxicological information on pentane and other paraffins. In common with most other alkanes, the chief effects of inhalation at high concentrations of pentane vapor are narcosis, loss of deep tendon reflexes, and induction of coma. Irritation of the respiratory passages can occur at much lower concentrations. The data on the toxicity which follow apply primarily, if not exclusively, to n-pentane.

According to Flury and Zernik,⁽⁴⁾ exposure to pentane at 130,000 ppm for 30 minutes was fatal to mice. A 5-minute exposure to n-pentane at 128,000 ppm for 5 minutes produced deep anesthesia in mice; respiratory arrest occurred in one of the four animals during exposure.⁽⁵⁾ After inhaling 90,000 to 120,000 ppm, narcosis occurs in mice in 5 to 60 minutes.⁽⁶⁾ Mice exposed at 32,000 to 64,000 ppm n-pentane for 5 minutes showed signs of respiratory irritation and became lightly anesthetized during the recovery period.⁽⁵⁾ After exposure to no more than 16,000 ppm for 5 minutes, no effects were observed in mice.⁽⁵⁾

Human Studies

When volunteers inhaled 5000 ppm pentane for 10 minutes, no mucous membrane irritation or other symptoms were recorded.⁽⁷⁾ Volunteers suffered from painful burning sensations accompanied by itching after topical application of pentane; after 5 hours, blisters formed on the treated areas.⁽⁸⁾ The aspiration hazard of pentane is considerably less than that of kerosene, octane, nonane, or decane.⁽⁹⁾

A NIOSH criteria document on alkanes⁽⁸⁾ contains little additional information on the toxicity of pentane. Among the six reports of polyneuropathy in workers chronically exposed to hydrocarbon vapors discussed by NIOSH,⁽⁸⁾ there was only one in which the solvent involved did not contain hexane as a major ingredient. Gaultier et al.⁽¹⁰⁾ mentioned five cases of neuropathy among employees of a belt manufacturing shop in France where the solvent believed responsible contained 80% pentane, 14% heptane, and 5% hexane. The symptoms in three of the cases consisted of anorexia, asthenia, paresthesia, fatigue, and bilateral symmetrical muscle failure found mostly in the legs. Electromyographic and nerve conduction studies confirmed the

damage to the peripheral nerves.

TLV Recommendation

There are few data upon which to base the TLV for pentanes. Controlled human exposures at 5000 ppm pentane for 10 minutes failed to cause the mucous membrane irritation and narcosis⁽⁷⁾ that were observed in mice exposed at 32,000 ppm n-pentane.⁽⁸⁾ Accordingly, a TLV-TWA of 600 ppm, with a STEL of 750 ppm is recommended for pentanes, limits which should provide a substantial margin of safety against narcotic and irritative effects. In view of the report by Gaultier et al.,⁽¹⁰⁾ however, the possibility that chronic exposure to high concentrations may lead to polyneuropathy cannot be ruled out altogether. Because of the otherwise substantially lower toxicity of pentane, in comparison with hexane, it is believed that such effects, if they occur, would require gross exposures, and the 600 ppm TWA and the 750 ppm STEL are expected to provide adequate protection against development of axonopathies. Additional information on the pharmacokinetics and metabolic fate of pentane in comparison with those for n-hexane are required for a rigorous evaluation of the neurotoxic potential of the pentane isomers.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 600 ppm and a 15-minute STEL of 750 ppm for pentane. OSHA concluded that these limits would protect exposed workers from the narcosis long known to be associated with pentane exposure.⁽¹¹⁾ The OSHA PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH established a REL-TWA of 120 ppm with a 15-minute ceiling limit of 610 ppm for pentane. NIOSH recommended the same occupational limits (TWA of 350 mg/m³ [equivalent to 120 ppm for pentane] and ceiling of 1800 mg/m³ [equivalent to 610 ppm for pentane]) for all C₅-C₈ alkanes as for the neuropathic alkane n-hexane.⁽⁸⁾ NIOSH [Ex 8-47, Table N2] did not concur with the OSHA PEL based on their belief that polyneuropathy may be caused by other alkanes, or mixtures of alkanes, and their isomers.⁽¹²⁾ NIOSH established an IDLH value of 15,000 ppm for this substance.

ACGIH Rationale for TLVs that Differ from the PEL or REL: Based on the information published to date, the ACGIH believes that all C₅-C₈ alkanes are not equipotent neurotoxins and that the neuropathies noted following exposures to mixtures of pentane, hexane, heptane, and octane are predominantly, if not entirely, due to the hexane content. Although the possibility that chronic exposure to high concentrations of pentane, heptane, and/or octane may lead to polyneuropathy cannot be ruled out altogether, there are no specific data on these compounds other than hexane which support their role

as etiologic agents in the pathogenesis of central-peripheral distal axonopathy.

NIOSH⁽⁸⁾ recommended the same RELs for all the alkanes: pentane, hexane, heptane, and octane. The rationale for this recommendation was not stated clearly, but the inference was that polyneuropathy was a general effect of paraffin hydrocarbon exposure. Such a rationale would ignore the observations that n-hexane and methyl n-butyl ketone (see the TLV Documentation for Methyl n-Butyl Ketone) are both metabolized to 2,5-hexanedione and, thus, have a similar neurotoxic mechanism of action.⁽¹³⁾

NTP Studies: Pentane was negative in the *Salmonella* assay. NTP has not conducted other genetic toxicology, other short-term toxicology, metabolism, or long-term toxicology and carcinogenesis bioassays on n-pentane.

Other Nations

Australia: 600 ppm, STEL 750 ppm (1990); Federal Republic of Germany: 1000 ppm, short-term level 2000 ppm, 60 minutes, 3 times per shift (for all isomers) (1991); Sweden: 600 ppm, short-term value 750 ppm, 15 minutes (for all isomers) (1990); United Kingdom: 600 ppm, 10-minute STEL 750 ppm (for all isomers) (1991).

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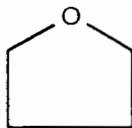
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TETRAHYDROFURAN

CAS: 109-99-9

Cyclotetramethylene oxide; Diethylene oxide; THF;
Tetramethylene oxide

C₄H₈O



TLV-TWA, 200 ppm (590 mg/m³)

TLV-STEL, 250 ppm (737 mg/m³)

1957-present: TLV-TWA, 200 ppm

1976-present: TLV-STEL, 250 ppm

1992: Documentation revised

Chemical and Physical Properties

Tetrahydrofuran (THF) is a colorless liquid with an acetone or ether-like odor. Odor thresholds of 2 ppm⁽¹⁾ to 7.4 ppm⁽²⁾ have been reported. Chemical and physical properties include:^(3,4)

Molecular weight: 72.10

Specific gravity: 0.8892 at 20°C

Melting point: -108.5°C

Boiling point: 66°C

Vapor pressure: 145 torr at 20°C

Flash point: -14.5°C, closed cup

Solubility: miscible with water, alcohols, ketones, esters, ethers, and hydrocarbons

Stability: upon contact with air, THF may decompose into explosive peroxides and carbon monoxide

Major Uses or Sources of Occupational Exposure

Tetrahydrofuran is a solvent for natural and synthetic polymers and resins, particularly polyvinyl chloride and vinylidene chloride copolymers. It is used in the manufacture of lacquers, glues, paint, and ink; it has found utility as an electrolytic solvent in the Grignard reaction-based production of tetraethyl and tetramethyl lead, as a chemical intermediate, and in wetting and dispersing of textiles.⁽⁵⁾ According to the 1981-1983 National Occupational Exposure Survey,⁽⁶⁾ approximately 356,000 U.S. workers were potentially exposed each day to THF.

Animal Studies

Acute

The acute toxicity of THF has been summarized.⁽⁷⁾ The oral LD₅₀ for THF is reported as 2.3 ml/kg (2045 mg/kg) in 14-day-old male rats and as 3.6 and 3.2 ml/kg in young adult and older adult rats, respectively.⁽⁸⁾ The

single oral lethal dose in rabbits was 2500 mg/kg of a 20% solution.⁽⁹⁾ DiVincenzo and Krasavage⁽¹⁰⁾ found no liver damage in guinea pigs injected intraperitoneally with 500 mg/kg THF.

A single 4-hour inhalation of THF in rabbits in the range of 100 to 12,000 ppm resulted in a transient dose-related decrease of tracheal ciliary activity.⁽¹¹⁾ Single or repeated exposures have been associated with cytolytic hepatitis and fatty degeneration of the liver.⁽¹²⁾

Stoughton and Robbins⁽¹³⁾ found concentrations of THF greater than 25,000 ppm were required to produce anesthesia. The anesthetic properties were rather poor in that onset was delayed and recovery poor; this was accompanied by pronounced hypotension and marked respiratory hyperpnea. There was a narrow margin of safety between anesthesia and death in dogs and mice. Other investigators have reported anesthetic⁽¹⁴⁾ and neuropharmacological⁽¹⁵⁾ effects induced by tetrahydrofuran.

THF was irritating to rabbits when applied topically in aqueous solutions exceeding 20% concentration.⁽¹⁶⁾

Subchronic

Lehmann and Flury⁽¹⁶⁾ reported irritation of the upper respiratory tract and found evidence for hepatic and renal injury in animals that inhaled concentrations of THF greater than 3000 ppm, 8 hours/day for 20 days.

Subsequent studies⁽¹⁷⁾ showed that when dogs inhaled 200 ppm THF 6 hours/day for 3 to 4 weeks, an observable effect on pulse pressure was recorded; however, no demonstrable histopathologic changes were found despite extended exposure of 9 weeks, followed by an additional 3-weeks exposure at up to 400 ppm. In contrast to previous reports,⁽¹⁶⁾ THF failed to irritate the skin and no evidence for skin sensitization was noted.⁽¹⁷⁾ Greater validity has been ascribed for the contemporary results than those previously reported, due in part to the greater numbers of animals tested.

Male rats that inhaled more than 5000 ppm THF for 12 weeks at 4 hours/day showed signs of systemic intoxication, skin and respiratory tract irritation, liver function disturbance, and abnormalities in glucose metabolism.⁽¹⁸⁾ Although systemic effects were not observed after similar exposures at lower concentrations, slight respiratory tract irritation occurred in some rats that inhaled concentrations less than 200 ppm.

Muscle acetylcholinesterase activity increased in a concentration-dependent manner in male rats that inhaled 200, 1000, or 2000 ppm for 18 weeks at 6 hours/day.⁽¹⁹⁾ THF concentrations in brain and peripheral fat appeared to decrease after 2 weeks. At 200 ppm, hepatic protein and mixed function oxidase activity were increased. At 2000 ppm, liver function was inhibited. Increased skeletal muscle succinate dehydrogenase activity was noted. In a 13-week inhalation study,⁽²⁰⁾ ataxia was reported in rats at 5000 ppm and narcosis was reported in mice at 1800 ppm.

Hepatocytomegaly developed in mice of both sexes at 5000 ppm; uterine atrophy and degeneration of the adrenal cortex occurred in the female mice.⁽²⁰⁾

When rats were exposed at 200 ppm THF, 4 hours/day, 5 days/week, between 12 and 24 weeks of age, slight damage to the nasal and tracheal epithelium was noticed. Similar exposures at 1000 ppm THF caused severe damage to the same tissues, decreased the number of cilia, and produced vacuolization and an increase in the numbers of dense granules in the epithelial cytoplasm.⁽²¹⁾

Reproductive/Developmental

Mast et al.⁽²²⁾ exposed rats and mice 6 hours/day, 7 days/week on gestational days 6 to 19 for rats and gestational days 6 to 17 for mice at 600, 1800, or 5000 ppm THF. Pregnant mice that inhaled 5000 ppm THF died; mice that inhaled 1800 ppm were sedated. The only treatment-related effects seen in the offspring were reduced fetal body weight and reduced ossification of the sternbrae, signs indicative of general growth and developmental delay. The maternal no-observed-adverse-effect level (NOAEL) for both species was 1800 ppm; the NOAEL for developmental toxicity was 1800 ppm in rats and 600 ppm in mice.

Genotoxicity Studies

Tetrahydrofuran was not mutagenic in *Salmonella typhimurium* TA100, at 50 μ l per plate.⁽²³⁾ Tetrahydrofuran failed to induce sex-linked recessive lethals in *Drosophila melanogaster* either by ingestion or injection.⁽²⁴⁾

Pharmacokinetic/Metabolism Studies

In vitro studies indicated that THF was first hydroxylated by the microsomal enzymes and further cleaved to the straight chain fatty acid in the presence of cytosol.⁽²⁵⁾ High concentrations (10^{-2} M) of THF inhibited the *in vitro* activity of rat hepatic cytochrome P-450 by 80%.⁽²⁶⁾

When healthy volunteers were exposed at 100 or 400 ppm THF in air, the percentage of expired THF was 35% in males with normal breathing, 25% in males with deep breathing, and 19% in females with deep breathing.⁽²⁷⁾ Three-hour exposures at 50 ppm THF resulted in 40% expiration of THF in males with normal breathing and 27% in males with deep breathing. The elimination half-life of THF was 30 minutes. In subjects exposed at 50 ppm THF in air for 6 hours, traces of THF were present at 3 hours after the end of exposure. In individuals exposed at 200 ppm THF for 3 hours, THF blood concentrations were higher at 1 hour after the end of exposure than immediately after cessation of exposure.⁽²⁷⁾

Human Studies

Exposure to THF has been reported to be irritating to the skin, eyes, and mucous membranes; no specific

concentration(s) for irritation has been described. Individuals exposed to high concentrations of THF have elevated circulating liver enzymes and have complained of nausea, tinnitus, and occipital headache.^(13,16,28,29) Liver biopsy confirmed fatty degeneration and siderosis along with elevated gamma glutamyl transferase and alanine aminotransferase occurred in one adult male occupationally exposed to THF.⁽¹⁵⁾

Viader et al.⁽³⁰⁾ examined a polyvinyl chloride (PVC) pipe fitter who worked in confined spaces using methyl ethyl ketone (MEK) and a glue containing 60% THF. The patient exhibited effects on the peripheral nervous system that resolved 2 months after exposure ceased. The investigators considered that these effects were most likely the result of occupational exposure to MEK or to the combined MEK and THF exposures.

Juntunen et al.⁽²⁹⁾ reported the case of a PVC pipe insulator whose most recent exposure to THF occurred over 2 weeks in a poorly ventilated, confined space. After hospitalization for acute appendicitis with enflurane anesthesia, the patient developed cerebral convulsions. The authors⁽²⁹⁾ suggested that the interaction of the anesthetic and occupational exposure to THF may have contributed to the onset of the convulsions.

Immunoglobulin-A nephropathy in a plumber fitting PVC pipe in a confined space with THF short-term exposures ranging from 389 to 757 ppm was reported by Albrecht et al.⁽³¹⁾ MEK in small amounts and unmeasured cyclohexanone were also present. The authors⁽³¹⁾ suggested that massive short-term exposure may have exacerbated predisposition to renal disease.

Two cases of occupational exposure to THF were reported by Garnier et al.⁽³²⁾ The symptoms included irritation of mucous membranes, nausea, headache, dizziness, and possible cytolytic hepatitis. The effects on mucous membranes and the central nervous system (CNS) resolved within a few hours after cessation of exposure.

Elevated aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase activities were considered indicative of transient hepatic involvement.

TLV Recommendation

Early studies^(16,17) demonstrated that THF is an upper respiratory tract irritant to animals exposed at concentrations > 400 ppm. Narcosis has been observed in animals and humans exposed to THF in air at concentrations on the order of 25,000 ppm.⁽¹³⁾ Accordingly, a TLV-TWA of 200 ppm has been recommended for THF since 1957, and a STEL of 250 ppm was added in 1976. These values are recommended to minimize the potential for irritation to upper respiratory tract tissues and to provide a margin of safety against THF-induced systemic effects. However, given the epithelial changes found in the respiratory

epithelium of rats that inhaled 200 ppm 4 hours/day, 5 days/week,⁽¹⁹⁾ and in view of the well-known differences in rodent and human anatomical parameters which contribute to upper airway absorbed dose and the associated response, the margin of safety afforded by the TLV for this substance is currently under review by the TLV Committee.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA for tetrahydrofuran of 200 ppm and a STEL of 250 ppm. OSHA concluded that these combined limits were necessary to reduce the potential risk of acute and chronic systemic effects associated with exposure to tetrahydrofuran.⁽³³⁾ The OSHA PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N1] established a REL-TWA of 200 ppm and a 250 ppm STEL by concurrence with the OSHA PEL for tetrahydrofuran.⁽³³⁾ NIOSH established an IDLH value of 20,000 ppm, the lower explosive limit (LEL) in air for tetrahydrofuran.

NTP Studies: NTP completed prechronic oral gavage and inhalation studies of tetrahydrofuran in male and female Fischer-344 rats and B6C3F1 mice. No chronic gavage study was scheduled; THF has been scheduled for chronic inhalation bioassay. Tetrahydrofuran failed to induce a significant mutagenic response in the *Salmonella* assay or in the *Drosophila* test for the induction of sex-linked recessive lethal mutations; in cultured Chinese hamster ovary (CHO) cells, there was no indication of induction of chromosomal aberrations or sister-chromatid exchanges.

Other Nations

Australia: 200 ppm, STEL 250 ppm (substance under review) (1990); **Federal Republic of Germany:** 200 ppm, short-term level 1000 ppm, 30 minutes, twice per shift, Pregnancy Group C, no reason to fear a risk of damage to the developing embryo or fetus when MAK and BAT values are adhered to (1992); **Sweden:** 100 ppm, short-term value 150 ppm, 15 minutes (1990); **United Kingdom:** 200 ppm, 10-minute STEL 250 ppm (1991).

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