TOXICOLOGICAL EVALUATION OF LIQUIDS PROPOSED FOR USE
IN DIRECT CONTACT LIQUID-LIQUID HEAT EXCHANGERS FOR
SOLAR HEATED AND COOLED BUILDINGS

R. M. Buchan
J. R. Majestic
R. Billau

September 1976

Work Performed Under Contract No. EY-76-S-02-2867

Solar Energy Applications Laboratory
Colorado State University
Fort Collins, Colorado

ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION
Division of Solar Energy

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency Thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.

NOTICE

This report was prepared as an account of work sponsored by the United States Government. Neither the United States nor the United States Energy Research and Development Administration, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness or usefulness of any information, apparatus, product or process disclosed, or represents that its use would not infringe privately owned rights.

This report has been reproduced directly from the best available copy.

Available from the National Technical Information Service, U. S. Department of Commerce, Springfield, Virginia 22161

Price: Paper Copy \$9.00 (domestic)
\$11.50 (foreign)
Microfiche \$3.00 (domestic)
\$4.50 (foreign)

TOXICOLOGICAL EVALUATION OF LIQUIDS
PROPOSED FOR USE IN DIRECT CONTACT
LIQUID-LIQUID HEAT EXCHANGERS FOR
SOLAR HEATED AND COOLED BUILDINGS

Topical Report

Roy M. Buchan, Joe R. Majestic, and Robin Billau

September, 1976

Prepared For

Energy Research and Development Administration
under Contract No. E(11-1)-2867

Solar Energy Applications Laboratory
Colorado State University
Fort Collins, Colorado 80523

NOTICE
This report was prepared as an account of work sponsored by the United States Government. Neither the United States nor the United States Energy Research and Development Administration, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness or usefulness of any information, apparatus, product or process disclosed, or represents that its use would not infringe privately owned rights.

TABLE OF CONTENTS

	<u>Page</u>
FOREWORD.	10
SUMMARY	16A
Additional Discussion of Table 1.	16F
Parameters Listed in Table 1.	16I
Additional Comments	16R
Acknowledgement	16T

TABLE OF CONTENTS - (Continued)

PageTOXICOLOGICAL EVALUATIONS

The following liquids are listed in order of increasing toxicity:

DIBUTYL PHTHALATE

Abstract-----	17
Chemical Properties-----	18
Hygienic Standards-----	18
General Toxicology-----	18
Acute Toxicity-----	20
Chronic Toxicity-----	22
Environmental Toxicology-----	23
Recommendations-----	24
References-----	25

BUTYL BENZYL PHTHALATE

Abstract-----	26
Chemical Properties-----	27
Hygienic Standards-----	27
General Toxicology-----	27
Acute Toxicity-----	29
Chronic Toxicity-----	30
Environmental Toxicology-----	32
Recommendations-----	33
References-----	34

O-DIMETHYL PHTHALATE

Abstract-----	35
Chemical Properties-----	36
Hygienic Standards-----	37
General Toxicity-----	37
Acute Toxicity-----	37
Chronic Toxicity-----	39
Human Toxicity-----	40
Environmental Toxicity-----	41
Recommendations-----	41
References-----	43

DIETHYL O-PHTHALATE

Abstract-----	44
Chemical Properties-----	45
Hygienic Standard-----	45
General Toxicology-----	46
Acute Toxicity-----	46
Chronic Toxicity-----	49
Human Toxicity-----	50
Environmental Toxicity-----	50
Recommendations-----	51
References-----	52

TABLE OF CONTENTS - (Continued)

	<u>Page</u>
PIPERONYL BUTOXIDE	
Abstract-----	53
Chemical Properties-----	54
Hygienic Standards-----	54
General Toxicology-----	55
Acute Toxicity-----	56
Chronic Toxicity-----	58
Environmental Toxicology-----	61
Recommendations-----	61
References-----	62
DI (2-ETHYLHEXYL) ADIPATE	
Abstract-----	63
Chemical Properties-----	64
Hygienic Standards-----	64
General Toxicology-----	65
Acute Toxicity-----	66
Chronic Toxicity-----	67
Environmental Toxicology-----	68
Recommendations-----	69
References-----	70
DI (2-ETHYL HEXYL) SEBACATE	
Abstract-----	71
Chemical Properties-----	72
Hygienic Standards-----	72
Toxicology-----	73
Recommendations-----	75
References-----	76
DIBUTYL SEBACATE	
Abstract-----	77
Chemical Properties-----	78
Hygienic Standards-----	78
Toxicology-----	78
Recommendations-----	80
References-----	81
PETROLATUM	
Abstract-----	82
Chemical Properties-----	83
Hygienic Standards-----	83
General Toxicity-----	83
Acute Toxicity-----	84
Chronic Toxicity-----	85
Environmental Toxicology-----	86
Recommendations-----	86
References-----	87

TABLE OF CONTENTS - (Continued)

	<u>Page</u>
ALLYL CAPROATE	
Abstract-----	88
Chemical Properties-----	89
Hygienic Standards-----	89
Background-----	89
Acute Toxicity-----	90
Chronic Toxicity-----	90
Human Toxicity-----	91
Environmental Toxicology-----	91
Recommendations-----	91
References-----	92
ETHYL CINNAMATE	
Abstract-----	93
Chemical Properties-----	94
Hygienic Standards-----	94
Toxicity-----	94
Recommendations-----	95
References-----	96
ACETYL TRIBUTYL CITRATE	
Abstract-----	97
Chemical Properties-----	98
Hygienic Standard-----	98
General Toxicology-----	98
Acute Toxicity-----	99
Chronic Toxicity-----	100
Environmental Toxicology-----	101
Recommendations-----	101
References-----	102
TRIBUTYL CITRATE	
Abstract-----	103
Chemical Properties-----	104
Hygienic Standards-----	104
General Toxicology-----	104
Acute Toxicity-----	105
Chronic Toxicity-----	106
Environmental Toxicology-----	107
Recommendations-----	108
References-----	109
METHYL HEPTENONE	
Abstract-----	110
Chemical Properties-----	111
Hygienic Standards-----	111
Toxicity-----	111
Environmental Toxicology-----	112
Recommendations-----	113
References-----	113

TABLE OF CONTENTS - (Continued)

	<u>Page</u>
ISOBUTYL SALICYLATE	
Abstract-----	114
Chemical Properties-----	115
Hygienic Standards-----	115
Background-----	115
General Toxicity-----	116
Environmental Toxicity-----	116
Recommendations-----	116
References-----	117
BUTYL OLEATE	
Abstract-----	118
Chemical Properties-----	119
Hygienic Standards-----	119
Toxicology-----	119
Recommendations-----	121
References-----	121
METHYL PHENYL ACETATE	
Abstract-----	122
Chemical Properties-----	123
Hygienic Standards-----	123
Toxicology-----	123
Recommendations-----	125
References-----	126
BENZYL FORMATE	
Abstract-----	127
Chemical Properties-----	128
Hygienic Standards-----	128
Toxicology-----	129
Recommendations-----	130
References-----	131
METHYL BENZOATE	
Abstract-----	132
Chemical Properties-----	133
Hygienic Standards-----	133
General Toxicology-----	134
Acute Toxicity-----	134
Chronic Toxicity-----	136
Human Toxicity-----	136
Environmental Toxicology-----	136
Recommendations-----	137
References-----	138
ETHYL BENZOATE	
Abstract-----	139
Chemical Properties-----	140
Hygienic Standards-----	140
General Toxicology-----	141
Acute Toxicity-----	141
Human Toxicity-----	142

TABLE OF CONTENTS - (Continued)

	<u>Page</u>
Environmental Toxicity-----	143
Recommendations-----	143
References-----	144
 ISOBUTYL ISOBUTYRATE	
Abstract-----	145
Chemical Properties-----	146
Hygienic Standards-----	146
General Toxicity-----	146
Acute Toxicity-----	147
Chronic Toxicity-----	148
Environmental Toxicology-----	148
Recommendations-----	148
References-----	149
 PERCHLOROETHYLENE	
Abstract-----	150
Chemical Properties-----	151
Hygienic Standard-----	152
General Toxicology-----	152
Acute Toxicity-----	153
Chronic Toxicity-----	156
Human Toxicity-----	156
Environmental Toxicology-----	160
Recommendations-----	160
References-----	161
 1,1,2 - TRICHLOROETHANE	
Abstract-----	163
Chemical Properties-----	164
Hygienic Standards-----	165
General Toxicology-----	165
Acute Toxicity-----	166
Chronic Toxicity-----	169
Environmental Toxicology-----	170
Recommendations-----	171
References-----	172
 BENZYL CHLORIDE	
Abstract-----	173
Chemical Properties-----	174
Hygienic Standards-----	174
Background-----	175
Acute and Chronic Toxicity-----	175
Environmental Toxicology-----	177
Recommendations-----	177
References-----	178

TABLE OF CONTENTS - (Continued)

	<u>Page</u>
THERMINOL 55	
Abstract-----	179
Chemical Properties-----	180
Hygienic Standards-----	180
General Toxicology-----	180
Acute Toxicity-----	182
Chronic Toxicity-----	183
Environmental Toxicology-----	183
Recommendations-----	184
References-----	184
O-DICHLOROBENZENE	
Abstract-----	185
Chemical Properties-----	186
Hygienic Standards-----	187
General Toxicology-----	187
Acute Toxicity-----	189
Chronic Toxicity-----	191
Environmental Toxicology-----	192
Recommendations-----	194
References-----	195
ORTHO-PHENETIDINE	
Abstract-----	196
Chemical Properties-----	197
Hygienic Standards-----	197
General Toxicity-----	197
Acute and Chronic Toxicity-----	198
Human Toxicity-----	198
Environmental Toxicology-----	199
Recommendations-----	199
References-----	200
DIVINYL BENZENE	
Abstract-----	201
Chemical Properties-----	202
Hygienic Standards-----	202
Toxicology-----	202
Recommendations-----	206
References-----	206
META-CHLOROANILINE	
Abstract-----	207
Chemical Properties-----	208
Hygienic Standards-----	208
General Toxicity-----	208
Acute Toxicity-----	209
Chronic Toxicity-----	210
Human Toxicity-----	211
Environmental Toxicology-----	211
Recommendations-----	212
References-----	213

TABLE OF CONTENTS - (Continued)

	<u>Page</u>
ORTHO NITROTOLUENE	
Abstract-----	214
Chemical Properties-----	215
Hygienic Standards-----	215
Toxicology-----	216
Recommendations-----	219
References-----	220
CREOSOTE COAL TAR	
Abstract-----	221
Chemical Properties-----	222
Hygienic Standards-----	222
General Toxicology-----	222
Acute Toxicity-----	223
Chronic Toxicity-----	225
Environmental Toxicology-----	228
Recommendations-----	229
References-----	230
ACETYLENE TETRABROMIDE	
Abstract-----	231
Chemical Properties-----	232
Hygienic Standards-----	232
General Toxicology-----	232
Acute Toxicity-----	234
Chronic Toxicity-----	235
Environmental Toxicology-----	236
Recommendations-----	236
References-----	237
CRESYL DIPHENYL PHOSPHATE	
Abstract-----	238
Chemical Properties-----	239
Hygienic Standards-----	239
General Toxicology-----	239
Acute Toxicity-----	240
Chronic Toxicity-----	242
Environmental Toxicology-----	242
Recommendations-----	243
References-----	244
TRI-O-CRESYL PHOSPHATE	
Abstract-----	245
Chemical Properties-----	246
Hygienic Standards-----	247
General Toxicology-----	247
Acute Toxicity-----	248
Chronic Toxicity-----	253
Environmental Toxicology-----	255
Recommendations-----	256
References-----	258

FOREWORD

This report contains the results of the toxicological evaluation part of the project entitled, "Direct Contact Liquid-Liquid Heat Exchangers for Solar Heated and Cooled Buildings." Obviously any liquid otherwise suitable for use in such a device should be subjected to a toxicological evaluation. 34 liquids (24 denser than water, 10 less dense) have physical and chemical properties that would make them suitable for use in such a device. In addition to the complexity involved in selecting the most promising liquids from the standpoint of their chemical and physical properties is added the additional difficulty of also considering their toxicological properties. Some of the physical and chemical properties of these liquids are listed in Table 1. In Table 1, the liquids are listed in alphabetical order within groups, the denser than water liquids are listed first followed by those liquids less dense than water.

In general it is preferable that the liquid used in the direct contact liquid-liquid heat exchanger be insoluble in water, otherwise a considerable quantity of the liquid may be necessary just to satisfy the solubility requirements of the water heat storage. The amount of solubility that can be tolerated will depend on the price of the liquid.

The relative toxicity values listed in Table 1 were determined by Dr. Buchan and his associates as follows. A list was made with the first liquid listed being the most acceptable on a toxicological and safety basis, and the last liquid listed being the least acceptable. The first liquid listed was assigned the number 1, and the last listed was assigned the number 34. Therefore, the lower the relative toxicity number in Table 1, the more acceptable that liquid is on a toxicological and safety basis. The toxicological evaluations in this report are in order of increasing toxicity.

All of the toxicological evaluations were prepared by either Joe R. Majestic or Robin Billau under the direction of Dr. Roy M. Buchan of the Institute of Rural Environmental Health at Colorado State University. Mr. Majestic prepared the toxicological evaluations on dibutyl phthalate, butyl benzyl phthalate, piperonyl butoxide, di (2-ethylhexyl) adipate, di (2-ethylhexyl) sebacate, dibutyl sebacate, methyl phenylacetate, benzyl formate, 1,1,2-trichloroethane, Therminol 55, O-dichlorobenzene, divinyl benzene, ortho nitrotoluene, creosote coal tar, acetylene tetrabromide, cresyl diphenyl phosphate, and tri-O-cresyl phosphate. Robin Billau prepared the toxicological evaluations on the remaining 17 liquids.

John C. Ward, Professor of Civil Engineering
Principal Investigator

Table 1. Some physical and chemical properties of liquids that could be used in the direct contact liquid-liquid heat exchanger.

No.	Name	Molecular Weight	Solubility in water, % by weight	Vapor density (air = 1)	Relative toxicity (1 = least toxic in, table, etc.)
1	acetylene tetrabromide	346	0.065	11.92	32
2	acetyl tributyl citrate	402	insoluble		12
3	benzyl chloride	127	insoluble	4.36	24
4	benzyl formate	136	very low	4.7	18
5	butyl benzyl phthalate		insoluble		2
6	meta-chloroaniline	128	insoluble		29
7	creosote coal tar	*	slightly soluble		31
8	cresyl diphenyl phosphate	337	insoluble		33
9	dibutyl phthalate	278	0.45		1
10	ortho-dichlorobenzene	147	insoluble		26
11	diethyl 0-phthalate	222	insoluble		4
12	0-dimethyl phthalate	194	0.5		3
13	ethyl benzoate	150	insoluble	5.2	20
14	ethyl cinnamate	176	insoluble		11
15	isobutyl salicylate	194	insoluble		15
16	methyl benzoate	136	insoluble	4.7	19

Table 1. Continued

No.	Name	Molecular Weight	Solubility in water, % by weight	Vapor density (air = 1)	Relative toxicity (1 = least toxic in, table, etc.)
17	methyl phenylacetate	150	insoluble		17
18	ortho nitrotoluene	137	insoluble		30
19	perchloroethylene	166	insoluble	5.7	22
20	ortho-phenetidine	137	slightly soluble		27
21	piperonyl butoxide	338	insoluble		5
22	tributyl citrate	360	<0.002		13
23	1,1,2 - trichloroethane	133	0.44	4.6	23
24	tri-O-cresyl phosphate	368	insoluble		34
25	allyl caproate	156			10
26	butyl oleate	339	insoluble		16
27	dibutyl sebacate	314	insoluble		8
28	di (2 ethylhexyl) adipate	371	insoluble		6
29	di (2-ethylhexyl) sebacate	427	0.02		7
30	divinyl benzene	130			28
31	isobutyl isobutyrate	144	0.5	5	21

Table 1. Continued

No.	Name	Molecular Weight	Solubility in water, % by weight	Vapor density (air = 1)	Relative toxicity (1 = least toxic in, table, etc.)
32	methyl heptenone	126	insoluble		14
33	petrolatum	*	insoluble		9
34	therminol 55		negligible		25

* varies with purity

The relative toxicity values can be grouped as follows:

- 1 - 9 Recommended for use as a heat exchange liquid in solar heating and cooling systems.
- 10-18 Recommended for use in solar energy heating and cooling systems, but preference should be given to those chemicals more thoroughly researched and determined to be toxicologically safe.
- 19-21 Toxicologically safe for use in solar heating and cooling systems, but poses other hazards that render it less suitable than those liquids with lower relative toxicity values.
- 22 Recommended for use in solar heating and cooling units only if extreme caution is observed in using this liquid.
- 23-34 Not recommended for use as a heat exchange liquid for solar heating and cooling systems.

Table 1. Continued

No.	Freezing point, °F	Boiling point, °F	Specific gravity	Cost, \$ per gallon	Viscosity at stated temperature centipoises	Flash point, °F	Auto-ignition point, °F	Odor
1	32	462	2.98	15.42		none		
2	-75	341	1.046	5.17	42.7 @ 77°F	400		none
3	-45	354	1.1	2.94		153	1,085	pungent
4	38	397	1.085	16.30				fruity-spicy
5	-31	698	1.116	2.98	65.2 @ 68°F	390		slight
6	14	443	1.223	8.17				sweet
7		400	1.07	5.18		165	637	
8	-36	734	1.208	6.91		450		very slight
9	-31	644	1.0484	3.32	20.3 @ 68°F	315	757	mild
10	- 8	356	1.307	3.25		151	1,198	pleasant
11	-41	568	1.120	3.46	4.18 @ 131°F	325		none
12	32	540	1.189	3.67	16.7 @ 68°F	295	1,032	none
13	-27	415	1.043	10.45		200		fruity
14	54	520	1.045	31.40				strawberry like

Table 1. Continued

No.	Freezing point, °F	Boiling point, °F	Specific gravity	Cost, \$ per gallon	Viscosity at stated temperature, centipoises	Flash point, °F	Auto-ignition point, °F	Odor
15	43	498	1.064	11.11				orchid
16	10	389	1.085	5.68		181		fragrant
17		424	1.062	9.82				
18	25	429	1.1629	1.36		223		
19	- 8	250	1.625	2.24		none		ether-like
20	- 4	442	1.065	8.05				
21		356	1.06	39.81		340		mild
22	- 4	451	1.04	6.65	31.9 @ 25°C	315	695	
23	-31	237	1.4432	3.27		none		sweet
24	-13	770	1.162	8.63	60 @ 25°C 5 @ 100°C	437	725	none
25		367	0.888	22.03				pineapple
26	-16	343	0.873	1.89		356		mild
27	12	660	0.936	8.59		350		none
28	-76	782	0.9268	3.79	13.7 @ 68°F	385		slight aromatic
29	-67	493	0.913	9.80		410		mild

Table 1. Continued

No.	Freezing point, °F	Boiling point, °F	Specific gravity	Cost, \$ per gallon	Viscosity at stated temperature, centipoises	Flash point, °F	Auto-ignition point, °F	Odor
30	-88	383	0.9289	6.89	1.09 @ 68°F	165		
31	-112	297	0.857	1.35		120		fruity
32	-87	343	0.860	34.81				citrus
33			0.920	1.11		444		none
34	-20	410	0.8867	2.80	1,610 @ 0°F 30.1 @ 100°F 5 @ 200°F 2.1 @ 300°F	355	675	slight

SUMMARY

By John C. Ward

It should be noted that the 34 liquids discussed in this report were selected from all the commercially available liquids marketed in this country. This is not to say that there are no other liquids commercially available that could be used in the direct contact liquid-liquid heat exchanger, but the liquids discussed in this report were identified as potential candidates by examining the information generally available to the scientific community.

In the initial selection cost was not considered relevant because cost can sometimes be influenced by demand and because costs may change dramatically in the future for any number of reasons. Therefore the initial selection was based entirely on the known physical and chemical properties. One obviously desirable physical property was that the liquids selected should be immiscible with water or at least have an extremely low solubility in water (the amount of solubility that can be tolerated obviously depends on cost). A difficulty experienced at the outset is the terminology regarding solubility in that it is not consistent and tends to be relative.

In addition, it is clearly necessary that the liquids proposed have densities that are significantly different from water at all temperatures of interest. Unfortunately densities were usually given at only one temperature (if at all), and these temperatures tended to be below the range of interest. As a result, the density difference between these liquids and water at all temperatures was now known at the outset. It can be said that, in general, this density difference varied with temperature. Another question still unresolved at this point in this project is: how much of a density difference is necessary, and how is performance related to density difference?

Other significant factors in the selection of these liquids were freezing and boiling temperatures. Any liquid that was to be considered a candidate had to have a boiling point greater than water. Freezing point criteria were generally more relaxed because of their potential usefulness anywhere in the world where freezing temperatures as high as even 54°F might conceivably not be a problem. However only 3 of the liquids discussed in this report have a freezing point higher than that of water.

With respect to cost, it is not known at this point in this project what is reasonable. Among other things, this depends on the solubility of the liquid in water. Even for those liquids that are insoluble in water, reasonable cost figures can not, in general, be prescribed at this point. For example, at least one commercially available solar collector contains a relatively large quantity of liquid and so costs that would be reasonable with other solar collectors might not be reasonable with this particular solar collector. Even where identical volumes of liquid are required in the collector liquid loop, the reasonable cost figure would be dependent on, among many

other things, the cost of the corresponding water antifreeze mixture necessary to prevent freezing, and this latter cost would depend on local climate. Other considerations affecting the determination of a reasonable cost figure include the cost of the heat exchanger and electric pump that are eliminated as well as the reduced collector area necessary and the reduced cost of the solar collector per unit area. The determination of a reasonable cost figure, because of its complexity, is believed to be an effort of such magnitude as to be another project in itself and consequently beyond the scope of this project. Nevertheless about 14 of the liquids listed have costs comparable to antifreeze-water mixtures consisting of 50% each ethylene glycol and water.

The relative volume of the immiscible liquid per unit volume of hot water storage will depend on system design and consequently can be highly variable. On the other hand, for a residential type solar system, the volume of liquid required in the collector liquid loop is probably around 30 gallons or so, so the total volume of immiscible liquid required would almost certainly be less than 100 gallons for most residential size solar systems.

Additional Discussion of Table 1

Because of page size limitations, it was necessary to group the information contained in Table 1 into 2 sets of data. The first set is on pages 11-13 and the second set is on pages 14-16. In both sets, the numbers used in the first column are utilized to tie information pertaining to the same liquid together. For example benzyl chloride (#3) has a freezing point of -45°F. The relative toxicity numbers appearing in the last column of the first set of data are not repeated in the second set of data.

The guiding philosophy in constructing Table 1 was to include any parameter that might conceivably have any relevance to this project and/or assist in the correct and complete identification of the liquid involved. As with any table of this sort, the same information is not available for all the liquids listed and therefore some columns contain only a few values.

While the liquids are listed in alphabetical order in Table 1, it should be noted that they are listed in order of increasing toxicity in the Table of Contents on pages 3-9. Because there may be very little difference in the relative toxicity of liquids listed adjacent to each other in the Table of Contents, the liquids have been grouped into 5 groups of liquids with roughly equivalent toxicities as follows: Group I (pages 17-87) liquids are recommended for use as a heat exchange liquid in solar heating and cooling systems. Group II (pages 88-131) liquids are recommended for use in solar energy heating and cooling systems, but preference should be given to those chemicals more thoroughly researched and determined to be toxicologically safe. Group III (pages 132-149) liquids are toxicologically safe for use in solar heating and cooling systems, but they pose other hazards that render them less suitable than those liquids with lower relative toxicity values. Group IV (pages 150-162) contains only perchloroethylene and

this liquid is recommended for use in solar heating and cooling units only if extreme caution is observed in using this liquid. Group V (pages 163-258) liquids are not recommended for use as a heat exchange liquid for solar heating and cooling systems.

There appears to be no clear cut relationship between density and toxicity for the liquids discussed in this report. This is indicated by the % distribution into the 5 groups:

Group	denser than water	lighter than water
I (least toxic)	21	40
II	25	30
III	8	10
IV	4	0
V (most toxic)	42	20
	100%	100%

Parameters Listed in Table 1

Molecular weight is given because it assists in the correct identification of the liquid.

Solubility is usually temperature dependent, so that the numerical value listed should be interpreted with caution because they are all near ordinary room temperature. The vague solubility terms such as very low, slightly soluble, and negligible also need cautious interpretation. Better and more precise solubility information is not given because it is not available.

The vapor density figures given indicate that those liquids have densities greater than air and consequently will collect in low locations. The magnitudes of the vapor densities given indicate that it is unlikely that vapors from those liquids will ever be lighter than air, regardless of temperature. All the vapor density figures available have been reported in Table 1.

The relative toxicity values apply only to the liquids listed in the table. The differences in relative toxicity between consecutive liquids may be relatively minor or quite significant as the previously discussed groupings indicate.

Some freezing points have not been given because they are not available. However, the crude determination of freezing points is so simple that it is believed that persons specifically interested in those liquids can easily experimentally determine the necessary information with sufficient precision for application in solar systems. The same remarks apply for the missing boiling point information. In both cases, it is believed that both the freezing and boiling points are probably satisfactory for solar system use in most instances.

The specific gravity figures given are all for temperatures near ordinary room temperature. These values can be expected to change significantly with temperature.

Viscosity is one of the most important parameters listed in Table 1. It will be noted that this information was available for only 10 of the liquids listed, and that the values given are not necessarily for the same temperature. Because of the extreme importance of this quantity, all information in the literature is given in Table 1. It should be also noted that the viscosity changes dramatically with temperature (see Number 34 on page 16 for example). The importance of viscosity is discussed further below, but it must be pointed out that in most liquid heating solar collectors, a large portion (if not all) of the resistance to flow is viscous resistance, and consequently pumping costs and liquid flow rates are both heavily dependent on viscosity. In addition viscosity determinations require special equipment and a significant amount of technical time.

Liquids with flash points that are too low are unsafe to use in solar systems, and this factor has been considered in the toxicity evaluations. However some liquids with low flash points have been included in the present study for the sake of completeness because it is conceivable they might be useful in relatively unique situations.

Autoignition temperatures are given even though they appear to be well above operating temperatures, because under stagnation conditions, temperatures in some evacuated glass tube collectors could conceivably exceed some of the autoignition temperatures given. In addition, this represents information one would want to consider in judging the relative usefulness and safety of the liquids listed.

Odors are also listed because it is important to know whether or not a given liquid has an odor (in case of leaks), and if so, what kind of odor. In addition some odors are more tolerable than others. While this latter point may represent a relatively insignificant weight in evaluating a liquid for the purpose proposed herein, it is nevertheless a consideration.

There has been no attempt whatsoever to group the parameters in Table 1 in any sort of order of importance for a number of reasons. In the first place, it is doubtful that any 2 qualified people would have the same opinion for a given application. In the second place, the specific application and/or solar system might change the order of importance. In the third place there are additional liquid properties not given in Table 1 (because the information is not available) that are more important for solar systems than many of the properties given.

The effect of the liquids listed on collector materials is, in general, unknown, but most should be compatible with the metals used in solar collectors. Certainly the corrosion problems associated with aqueous solutions are avoided. The chemical stability at operating temperatures is also generally unknown, but may be similar to ethylene glycol and other commercially available heat transfer liquids.

In order to use any of these liquids in a direct contact liquid-liquid heat exchanger, it is highly desirable to know all of the following 4 properties as a function of temperature: (1) density, (2) viscosity,

(3) specific heat, and (4) thermal conductivity. None of these 4 properties are known for any of these liquids as a function of temperature with the single exception of Therminol 55 which is a commercially available heat transfer liquid. Density and/or viscosity values may be given at a single temperature which is clearly inadequate. In general specific heat and thermal conductivity values are not available at any temperature.

As a consequence, the liquids selected from Table 1 for use in the pilot scale direct contact liquid-liquid heat exchanger required a substantial amount of laboratory work to establish these properties as a function of temperature. Density was the easiest property to establish as a function of temperature, but a great deal of technical time was expended on this task. Viscosity required the purchase of a significant quantity of laboratory equipment and also a large amount of technical time. Specific heat requires elaborate equipment not ordinarily readily available. Finally determination of thermal conductivity values as a function of temperature costs about \$350 per liquid tested. Nevertheless all 4 of these properties were experimentally determined as a function of temperature for all the liquids tested in the pilot scale direct contact liquid-liquid heat exchanger, and they will be given in the completion report for this phase of this project.

Additional Comments

O and Ortho are used interchangeably in the chemical names.

The toxicity discussion on Butyl Benzyl phthalate (pages 26-34) may raise some questions in the minds of some readers as to why this liquid is rated so low, especially in view of the doubts expressed about the chronic toxicity of the liquid. This liquid was tested in the pilot scale direct contact liquid-liquid heat exchanger.

One problem encountered during the course of this phase of the project is that different sources in some cases give somewhat different values for some of the properties in Table 1. There really is no reasonable way for the project personnel to decide which of 2 or more different values is correct. As a consequence some of the values given in the toxicological evaluations did not agree perfectly with the values given in Table 1. Instead of arbitrarily picking one value as correct and discarding the other value, it was decided to list both values and call attention to these discrepancies in this summary.

The flash point of O-Dimethyl Phthalate is given as 325°F in the writeup on page 36 and as 295°F in Table 1 (page 14). The odor of Di (2-Ethylhexyl) Sebacate is described as odorless on page 72 and is listed as mild in Table 1 (page 15).

Acknowledgement

Dr. Allen I. Michaels, Materials Science Division, Argonne National Laboratory, reviewed the first draft of this report. He noted several apparent errors or inconsistencies and made several suggestions for changes and additions. Most of these were incorporated and have improved the usefulness and clarity of the report.

TOXICOLOGICAL EVALUATION OF DIBUTYL PHTHALATE

June 10, 1976

ABSTRACT

Dibutyl Phthalate (DBP) belongs to a family of chemicals known as phthalic acid esters (PAE) that are of industrial importance as plasticizers. Along with being a popular plasticizer, DBP has also found use as an insect repellant. Toxicologically, DBP is almost inert. Its low order of toxicity, both acute and chronic has been attributed to its low molecular weight and solubility constant. With respect to occupational environmental exposure, the chemical presents insignificant hazards that are easily controlled. Environmentally, there is some question about DBP persistence in the environment and biomagnification in the food chain, however this question is not completely resolved and further research is required.

On the basis of toxicological information currently available, DBP is recommended for use as a heat exchange medium for solar heating and cooling.

I. Chemical Properties:

Name: Dibutyl Phthalate

Molecular formula: $C_6H_4 (COOC_4H_9)_2$

Molecular weight: 278.38 (1)

Synonyms: Dibutyl -1, 2 - benzenedi-carborylate, n - butyl, phthalate; Di - n - butyl phthalate; Di - o - butyl phthalate; Celluflex DBP; Elaol; Hexaplas; Palatinol C; Polycizer DBP; Staflex DBP; Witcizer 300.

Freezing point: $-31^{\circ}F$

Boiling point: $644^{\circ}F$

Specific gravity: 1.0484

Flash point: $315^{\circ}F$

Autoignition point: $757^{\circ}F$

Solubility: water - 0.45 g/100ml (2); alcohol, ether, benzene - soluble in all proportions (3)

Viscosity: 20.3 centipoises @ $68^{\circ}F$

Vapor pressure: <0.1 mm Hg @ $20^{\circ}C$ (4); 1.1 mm Hg @ $150^{\circ}C$

Volatility: $0.98 \text{ mg/cm}^2/\text{hour}$ @ $100^{\circ}C$ (4)

Appearance: colorless to yellowish, viscous liquid (4)

Stability: stable and inert, but hydrolyzed by alkalis (4)

II. Hygienic Standards:

TLV: air 5 mg/m^3 (OSHA standard 1910.93)

III. General Toxicology:

Dibutyl Phthalate (DPB) belongs to a family of compounds known as

phthalic acid esters (PAE). The PAE's became industrially important during and after World War II, especially in the area of plastics production. Dibutyl phthalate has had many applications including uses in safety glass, perfumes, printing inks, lacquers, textiles, solvents, and rubber (5). However, DBP has found greatest use as an insecticide and as a plasticizer. As an insecticide, DBP is a repellant for ticks and a quick acting toxicant for certain trombiculid mites. It resists washing and is, therefore, an effective impregnant for cloth and clothing (4). As a plasticizer, DBP is one of the most common plasticizers for nitro, ethyl, and benzyl celluloses. It is also the plasticizer of choice for polyvinyl acetate and polymethylmethacrylate and has long been used as a plasticizer for polyvinylchloride (6). Today, DBP is used primarily only as a plasticizer.

It is beneficial at this point to discuss the toxicology of the group of plasticizers known as PAE's, since all of these compounds have essentially the same toxicological properties. PAE's are manufactured by esterifying the alcohol corresponding to the required ester with phthalic anhydride (6,7). It is from this parent compound that PAE's obtain their toxicological properties. When phthalic anhydride comes into contact with moist mucous membrane or wet skin, it acts as a potent skin, eye, and upper respiratory irritant. Repeated contact in this manner can cause skin and pulmonary sensitization leading to allergic dermatitis and asthmatic attacks. The American Conference of Governmental Industrial Hygienists has established a TLV for phthalic anhydride of 2 ppm in air (6,7,8,9).

In general, PAE's exhibit the same toxicological properties as their parent compound, phthalic anhydride, but to a much lesser degree.

The difference in toxicity are believed to exist because PAE's are viscous liquids with low solubilities, while phthalic anhydride is a crystalline solid with considerably higher solubility. The relative toxicity of a PAE is based upon two factors. The first is solubility. The more soluble the PAE, the more biologically active and hence, the more toxic the compound (10). The second factor is molecular weight. Phthalic esters with high molecular weights have higher intrinsic toxicities than PAE's of lower molecular weight (8). As a group, PAE's are toxicologically significant from only two routes of exposure, respiratory and dermal. When PAE's are vaporized at high temperatures (above 200°C), or are dispersed in air as mists or sprays, extended periods of inhalation at high concentrations can result in pulmonary irritation and sensitization. The long range effect is depressed central nervous system activity, clinically diagnosed as toxic polyneuritis characterized chiefly by pain and numbness of the extremities (11). Dermal, PAE's are basically slight irritants. However, some have exhibited the property of absorption through the skin leading to their sensitizing effect that may cause allergic dermatitis in susceptible populations (9).

Dibutyl phthalate exhibits a toxicology characteristic to the rest of the PAE group, but at an extremely low order. Its relatively low molecular weight and solubility constant make it almost inert, however, it has exhibited some low acute and chronic toxicity.

IV. Acute Toxicity:

Because of its economic importance and the large volume of DBP consumed, much experimental data exists on its acute toxicity to lab animals. LD₅₀ values on a variety of animals and routes of exposure have been suggested and are summarized in Table 1.

TABLE 1.

Acute Toxicity of Dibutyl Phthalate: LD₅₀ in Animals

<u>Animal</u>	<u>Route of Exposure</u>	<u>LD₅₀, (g/kg)</u>
rat	oral*	>20
	oral	8
	oral	8-10
	oral	10
	oral	12.6
	intraperitoneal**	3.05 ml/kg
	intraperitoneal	8.0
mouse	intraperitoneal	4.0
rabbit	dermal***	20.0 ml/kg

* oral data from reference (12)

** intraperitoneal data from reference (8)

*** dermal data from reference (2)

The LD₅₀ values listed are high for all routes of exposure, indicating that acute toxic effects of DBP are negligible. Further examples can be cited to support this hypothesis. An industrial mishap led to oral ingestion of 10 g (140 mg/kg) of DBP by a chemical operator. Symptoms of nausea, dizziness, photophobia, lacrimation, and conjunctivitis occurred, but prompt recovery followed without complication (9). Dermal applications of DBP to rabbits at sublethal doses have been carried out to determine irritative response. Concentrations of 100 mg/ml injected intradermally produced mild responses at 10 and 15 minutes, and only a moderate response was seen after 26 minutes (11). Finally, a study conducted to determine the acute toxic effects of DBP via the respiratory route exposed cats at concentrations of 1 mg/liter for periods of 5.5 hours. Only slight nasal irritation resulted from this type of air borne exposure (2).

The acute toxic effects of DBP can be considered minimal, most certainly to animals and also to humans. Ingestion of relatively large doses produces only minor short term symptoms. DBP has been applied directly to the skin as an insect repellent since World War II with no acute adverse side effects, and seemingly no skin sensitization. Acute toxic effects of respiratory exposure are almost nonexistent.

V. Chronic Toxicity:

Information available on chronic toxicological effects of DBP is mainly from two long term ingestion studies with rats. Lefaux cites a study conducted by Smith, spanning one year, in which rats were fed concentrations of 0.01 percent, 0.05 percent, and 1.25 percent in their daily food (6). The rats receiving 0.01 and 0.05 percent showed no effects after 1 year. At a concentration of 1.25 percent, one half of the animals died in the first week. Lefaux further states that Bornmann, investigator in the second study, administered doses of 0.5 ml/kg and 1.0 ml/kg of DBP to rats twice a week for one year (6). No abnormalities of any kind were found at the end of this period that could be linked to DBP. These two studies indicate a very low order of chronic toxicity via ingestion of DBP.

A long term study on the carcinogenic properties of DBP was carried out by the Cancer Institute of France. Again rats were used and were fed daily from diets consisting of 100 mg, 300 mg, and 500 mg DBP per kilogram body weight. Rat populations studied over three and five generations showed no malignant tumors. Extrapolated to man, the findings indicate that a 70 kg man leading an active life could ingest as much as 300 mg DBP per day without carcinogenic risk (6). Other studies, however, have implicated DBP as a teratogen. DBP administered to pregnant

rats in large quantities (as much as one-third of the acute LD₅₀), has produced teratogenic effects (1,13). However, quantities administered to the rats were extremely large, and it is not likely that pregnant mothers would be exposed to such enormous quantities.

One other chronic study of interest, is a Russian study of respiratory exposure to PAE's in the industrial environment. The study followed 147 workers with exposure times of 6 months to 19 years. Exposure levels ranged from 1.7 to 66 mg/m³ of PAE vapors and aerosols, predominantly DBP. Noticeable effects were closely related to time of exposure, with clinical symptoms largely appearing in the form of a moderately pronounced toxic polyneuritis (14).

The chronic toxicity of DBP is a relatively little concern. Like other PAE's, DBP is of low order of toxicity because of its low molecular weight and solubility.

VI. Environmental Toxicology:

There has been in recent years, some concern over the buildup of PAE's in the environment. DBP has been found in soil, water, aquatic organisms, and in bovine tissues (15). Of main concern is the concentrations found in water, presumably from industrial waste discharges. Although, DBP does not present any great acute toxic hazard to marine life, there is evidence that many species of marine life can concentrate DBP as much as 1,400 times in their tissues in 14 days when the concentration of DBP in water is 0.1 µg/l (15). Such evidence hints that DBP can be biomagnified as it moves through the food chain.

The other unanswered question concerning PAE's in the environment is that of their biodegradability. Generally, they are believed to be as biodegradable as most biodegradable detergents (7). However, this

has been recently questioned and may prove not to be the case. If in fact, PAE's prove to not be as degradable as now expected, and if they undergo biomagnification in the food chain, hazards not realized today could be presented.

There is little threat of hazard in the occupational environment from DBP. Although some respiratory and dermal irritation can occur, and central nervous system disorders have resulted from long exposures at high concentrations, these ailments could be easily eliminated by control of DBP concentrations in the work environment using currently available engineering techniques. Medical monitoring of exposed personnel and good work hygiene would also prove beneficial (2,14).

VII. Recommendations:

Toxicologically, dibutyl phthalate (DBP) is suitable for use as a heat exchange medium for solar heating and cooling. It possesses a low order of toxicity, both acute and chronic and would present little health hazard to those occupationally involved in manufacture of the units, or to consumers who used them. Environmentally, there is some concern over the presence of PAE's that may be persistent and cause problems as they accumulate over time. Further research in this area is desirable to determine the most practical and efficient way to reduce PAE residues in the environment.

References

1. National Institute for Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances U.S. Government Printing Office. Washington, D.C. 1975.
2. Patty, F.A. Industrial Hygiene and Toxicology. Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
3. Weast, R.C. Handbook of Chemistry and Physics. Chemical Rubber Company. Cleveland. 1972.
4. National Academy of Sciences. Handbook of Toxicology Volume III: Insecticides. W.P. Saunders Company. Philadelphia. 1959.
5. Plunkett, E.R. Handbook of Industrial Toxicology. Chemical Publishing Company, Inc. New York. 1966.
6. Lefaux, René. Practical Toxicology of Plastics. Iliffe Books Ltd. London, England. 1968.
7. Graham, P.R. Phthalate Ester Plasticizers - Why and How They are Used. Environ. Health Perspectives. Exp. Issue No. 4. pp. 3-12. June, 1973.
8. Autian, J. Toxicity and Health Threats of Phthalate Esters: Review of Literature. Environ. Health Perspectives. Exp. Issue No. 4. pp. 3-26. June, 1973.
9. American Conference of Governmental Industrial Hygienists. Documentation of Threshold Limit Values. Third Edition, 1974.
10. Singh, A., et al. Teratogenicity of Phthalate Esters in Rats. Journal of Pharm. Science. Vol. 61, No. 1, pp. 51-55. 1972.
11. Calley, D., et al. Toxicology of a Series of Phthalate Esters. Journal of Pharm. Science, Vol. 55, No. 2, pp. 158-162. February, 1966.
12. Krauskopf, L.G. Studies on the Toxicity of Phthalates via Ingestion. Environ. Health Perspectives. Exp. Issue No. 3, pp. 61-72. January, 1973.
13. Dillingham, E.O. and Autian, J. Teratogenicity, Mutagenicity, and Cellular Toxicity of Phthalate Esters. Environ. Health Perspectives. Exp. Issue No. 3, pp. 81-89, January, 1973.
14. Melkov, L.E., et al. Health Status of Workers Exposed to Phthalate Plasticizers in the Manufacture of Artificial Leather and Films Based on PVC Resins. Environ. Health Perspectives. Exp. Issue No. 3, pp. 175-178. January, 1973.
15. Mayer, F.L. and Sanders, H.O. Toxicology of Phthalic Acid Esters in Aquatic Organisms. Environ. Health Perspectives. Exp. Issue No. 3 pp. 153-157. January, 1973.

TOXICOLOGICAL EVALUATION OF BUTYL BENZYL PHTHALATE

March 4, 1976

ABSTRACT

Based on the toxicological information gathered for this report, butyl benzyl phthalate is highly recommended as a heat exchange medium for solar heating and cooling.

Butyl Benzyl Phthalate belongs to a family of compounds known as phthalic acid esters (PAE) which in general exhibit a low order of toxicity. Butyl Benzyl Phthalate is slightly less toxic than some of the other PAE's which have found wider use. There are essentially no acute toxicological effects caused by butyl benzyl phthalate. Animal studies have established LD₅₀ values of 1.8 gm/kg for rats and 3.16 gm/kg for mice which are high enough to assume that acute effects to humans are negligible. Chronic effects have been noted and are directly related to concentration and time of exposure. Prolonged exposure at elevated concentrations have resulted in effects to the respiratory and nervous system, and the skin. Butyl benzyl phthalate vapor upon inhalation can induce pulmonary irritation, but more significantly acts as a central nervous system depressant that produces a moderately pronounced polyneuritis. Dermally, butyl benzyl phthalate is an irritant, and although never shown in man, can have a sensitizing effect in animals due to the absorption through the skin. There is no data to link butyl benzyl phthalate to carcinogenic, mutagenic, or teratogenic effects, although some of the other PAE's can cause teratogenicity at extremely high concentrations. The toxicological effect of butyl benzyl phthalate in the environment is not known, however some concern has been shown over the possibility that it may be persistent and accumulate in food chains.

Butyl Benzyl Phthalate

I. Chemical Properties -

Freezing Point: 31°F	Specific Gravity 1.116
Boiling Point: 698°F	Solubility (gm/100 gm H ₂ O) -
Flash Point: 390°F	Insoluble.
Molecular Formula - C ₄ H ₉ COOC ₆ H ₄ COO CH ₂ C ₆ H ₅	

II. Hygienic Standards -

There are presently no available standards for exposure to butyl benzyl phthalate.

III. General Toxicology -

Butyl Benzyl Phthalate belongs to a family of compounds known as phthalic acid esters (PAE), that have found widespread use in the plastic industry since World War II. Known as plasticizers, PAE's, are added to cellulose or vinyl resins to increase their flexibility and softness, and may comprise as much as 40% by weight of the final products. PAE's are manufactured by esterifying the alcohol corresponding to the required ester with phthalic anhydride (1,2). This is important to note, since any toxic effects that can be attributed to PAE's are derived from this compound. Phthalic anhydride is a potent skin, eye, and upper respiratory irritant and can cause skin and possibly pulmonary sensitization. Phthalic anhydride is relatively non-toxic in its normal state as a white crystalline solid. Its toxic effects result when the powder comes into contact with moist mucous membranes or wet skin. Repeated contact with the agent in this manner can result in allergic dermatitis and pulmonary sensitization, leading to asthmatic attacks. For these reasons, a Threshold Limit Value for phthalate anhydride has been established, by the American Conference of Governmental Industrial Hygienists, of 2 ppm or 12 mg/m³ (4,3,2,1).

While phthalic anhydride exhibits fairly marked toxicological effects, PAE's do not. In general, PAE's have a very low degree of toxicity. This difference is theorized to be due to the lack of solubility of PAE's. Whereas, solid phthalic anhydride is soluble, especially in warm or hot mediums, PAE's are generally insoluble in their liquid form (4,3). However, as a group, PAE's do possess some toxicological properties. The only two routes of exposure with any significance are respiratory and dermal. At high temperatures (above 200°C) PAE's are subject to vaporization and these vapors, either inhaled or in surface contact with the skin, are the main toxicological concern. The effects manifested by exposure to PAE's in this manner are closely parallel to those of phthalic anhydride, but to a much lesser degree. Pulmonary irritation and sensitization can result from inhalation of the vapors, but require high dosages over extended periods of time. A long range effect of vapor inhalation is depression of central nervous system activity, clinically diagnosed as toxic polyneuritis characterized chiefly by pain and numbness of the extremities (5). Dermal, PAE's are basically slight irritants. However, some have exhibited the property of absorption through the skin, leading to their sensitizing effect that may cause allergic dermatitis in susceptible populations. (4).

Butyl benzyl phthalate exhibits a toxicology characteristic to the PAE group. It is generally of a low order of toxicity, and in relation to the other compounds in its group, is an extremely mild toxicological agent. Although many studies have been conducted to determine the toxicological properties of PAE's, there is relatively little information on butyl benzyl phthalate, presumably because it is a low risk compound

However, there has been at least one laboratory study completed on the compound for each route of exposure (oral, dermal, respiratory, and intraperitoneal), which will be cited in subsequent areas of this paper.

IV. Acute Toxicity

Relatively little study has been done on the acute toxicity of butyl benzyl phthalate. The bulk of the information comes from separate studies by Calley, et al. (7) and Mallette and Von Haam (7). Both studies give an intraperitoneal LD₅₀ of butyl benzyl phthalate. The Calley study was done on Swiss Webster white mice and resulted in an LD₅₀ value of 3.16 gm/kg (5). The Mallette and Von Haam study was done on rats and indicated LD₅₀ values in excess of 1.8 gm/kg (7). The difference between the two values are marked, but even the lowest value does not indicate an extremely toxic effect.

Similarly, both studies measured acute dermal responses. Calley (5) intradermally injected rabbits with concentrations of 100 mg/ml and received no response in 10 minutes, a mild reaction in 15 minutes, and a moderate response in 26 minutes. Mallette and Von Haam (7) used a patch test method to apply the chemical directly to the skin of rabbits and humans. At 100% concentration, rabbits showed a moderate irritative response. Two weeks later sensitization tests showed a slight sensitizing effect at the same concentration. Exposures to humans were again directly to the skin by a patch test with concentrations of 10 percent butyl benzyl phthalate. Eighty-eight percent of the population showed no irritation response, while the 12% who were affected showed a moderate effect. None of the human tests showed a sensitizing effect after 2 weeks when exposed to the same concentrations (5,7).

No data is available on the acute toxicity of butyl benzyl phthalate by the oral or respiratory routes; however, chronic data for these routes is available and will be discussed below.

The acute toxicity of butyl benzyl phthalate is of a relatively low order. Reported LD₅₀ values are high enough to presume that human exposure would have to be unrealistically large before acute effects would be clinically noticeable. The irritative and sensitizing effects of the chemical through human dermal exposure are almost negligible on the acute level, but may prove more severe on a chronic basis. Finally, acute effects caused by inhalation of butyl benzyl phthalate vapor would seem to be nonexistent. Although no specific data exists to substantiate this assumption, the PAE's as a whole have a low volatility and thus are not easily vaporized minimizing exposure potential. Large amounts of vapor at extremely high concentrations would have to be generated before acute respiratory effects of butyl benzyl phthalate would be evident (3).

V. Chronic Toxicity

Little is known about the chronic toxicity of butyl benzyl phthalate. Although there is a concern that PAE's may be persistent in the environment, the complete spectrum of chronic toxicity of PAE's has not been widely explored. Most of the research that is available is for chronic exposure via the oral route. Only one study can be found on the chronic toxicity of butyl benzyl phthalate by ingestion. The report, unpublished, was conducted by Monsanto Company, a manufacturer of the compound (8). Rats and dogs were fed amounts of butyl benzyl phthalate in the ranges of 0.25% to 2.00%, of the daily diet for rats, and from 1% to 5% of the normal daily diet for dogs. Ninety days of continuous exposure in this manner showed little effect. Until butyl benzyl phthalate exceeded 1.0% of the daily diet for rats, no effect was shown. At 1.5% and 2.0%

a slight loss of growth rate was noted. Similar results were obtained for dogs. At 1.0%, 2.0%, and 5.0% of the daily diet, essentially no effects were noted. There were no deaths, no weight loss, and no effect on internal organ function (8).

One study was found on chronic exposure to PAE's of workers in the plastics industry. This Russian study followed 147 workers with exposure times of 6 months to 19 years. Exposure levels ranged from 1.7 to 66 mg/m³ of PAE vapors and aerosols. Although exposure was not limited to butyl benzyl phthalate, it was one of the chemicals found in the vapors and aerosols. Noticeable effects were closely related to years of exposure to PAE's. Clinical symptoms largely appeared in the form of a moderately pronounced toxic polyneuritis. An investigation of the sensory functions revealed an early lowering of the excitability of the vestibular and olfactory receptors, and of cutaneous sensitivity (6).

Nothing was found to link the butyl benzyl phthalate to teratogenic, mutagenic, and carcinogenic effects. In general, PAE's have been found to be noncarcinogenic in tests of chronic exposure through ingestion. However, some PAE compounds have caused teratogenic effects in lab animals. High concentrations of PAE's were needed to cause teratogenicity and it is unlikely that humans could be exposed to levels high enough to produce similar syndromes in expectant mothers (3,8).

In conclusion, present knowledge indicates that the chronic toxicity of butyl benzyl phthalate should be further researched. What data there is would seem to suggest that again, butyl benzyl phthalate is of a low order of toxicity and not of much concern in terms of chronic toxicity except possibly in the industrial environment.

VI. Environmental Toxicology

In the past few years, there has been a growing concern about the accumulation of PAE's in the environment. Over one billion pounds of PAE's are consumed in the United States per year, and PAE residues are beginning to show up in the environment (8). Of special concern is the wide distribution of PAE's in water bodies around the world. Since PAE's are being detected in waters far removed from industrial disposal sites, it is thought that PAE's may be released from plastic items that are disposed of in water (3). Just how detrimental these PAE's will be in years to come is not certain. Transport of PAE's through the food chain, and possible biomagnification of the residues must be a concern, especially since the residues have been found in the crustacean Daphnia magna. Crustaceans are an essential link in the aquatic food chain, and at least Daphnia has exhibited the ability to accumulate PAE residues up to 600 µg/kg in waters in which the concentration of PAE's was 0.1 µg/l (a 6,000-fold increase). The same study also showed that concentrations of only 3 µg/l significantly decreased growth and reproduction of the crustacean (3). In conflict to these results, however, a specific aquatic toxicity has been assigned to butyl benzyl phthalate of over 1000 ppm. This is an acute toxicity value, the concentration representing the amount needed to kill 50% of test aquatic organisms in 96 hours. This value, from a study conducted by Hann and Jensen is cited in the 1975 Registry of Toxic Effects of Chemical Substances, and is large enough to place butyl benzyl phthalate in a Grade 0 classification that translates to mean an insignificant hazard (9).

The real question, however, resolves around the ability of PAE's to be persistent in the environment, and whether or not they will be stored

by plants, animals, and humans, or metabolized and excreted. The question, for all practical purposes, is unanswered. One laboratory has shown butyl benzyl phthalate to be 99% biodegradable in 48 hours in a semicontinuous activated sludge system at a feeding rate of 5 mg/48 hrs. (2). Many would argue however that this figure is not valid and that actually PAE's are much more persistent than this might indicate. If indeed PAE's are rather persistent, one cannot overlook the possibility of accumulation in the food chain leading to biomagnification in man. If the possibility proves legitimate, some long range chronic effects in the general population that are yet undetected may lie ahead.

Occupationally, butyl benzyl phthalate is of little toxicological concern. Although some chronic effects have been shown in workers, via the respiratory and dermal routes, these exposures could easily be controlled by common industrial hygiene engineering control techniques. In addition to these engineering controls, close medical monitoring of exposed workers, transfer to jobs without exposure to butyl benzyl phthalate for extremely susceptible workers, and a good personal hygiene programs should be instituted (6,10). There are few other industrial hazards that can be connected to butyl benzyl phthalate. Danger of fire or explosion is slight even when exposed to heat or flame, and any fire that may erupt could be controlled with water (11).

VII. Recommendations

From a toxicological standpoint, butyl benzyl phthalate is suitable for use as a heat exchange medium for solar heating and cooling. Its low order of toxicity, both acute and chronic, make it an almost inert toxicological chemical. The only area of concern is the possible effect it could have on the environment and man if discarded residues prove

persistent. However, that there already is concern about this problem is encouraging. Research into this area, that will undoubtedly provide clearer understanding of the problem, and perhaps the necessary technology to control the disposal of butyl benzyl phthalate wastes, is now under way and will continue. Undoubtedly PAE's in general, and butyl benzyl phthalate in particular, can be controlled if and when they become of environmental consequence.

References

- 1) Lefaux, René. Practical Toxicology of Plastics. Iliffe Books Ltd, London, England. 1968.
- 2) Graham, P. R. Phthalate Ester Plasticizers - Why and How They Are Used. Environ. Health Perspectives. Experimental Issue No. 3 pp. 3-12. Jan. 1973.
- 3) Autean, J. Toxicity and Health Threats of Phthalate Esters; Review of the Literature. Environ. Health Perspectives. Experimental Issue No. 4 pp. 3-26. June, 1973.
- 4) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values. Third Edition, Second Printing, 1974.
- 5) Calley, D., et al. Toxicology of a Series of Phthalate Esters. Journal of Pharm. Sci. Vol. 55, No. 2. pp. 158-162. February 1966.
- 6) Melkov, L. E. et al. Health Status of Workers Exposed to Phthalate Plasticizers in the Manufacture of Artificial Leather and Films Based on PVC Resins. Environ. Health Perspectives. Experimental Issue No. 3 pp. 175-178, January 1973.
- 7) Mallette, F. S., and Von Haam, E. Studies on the Toxicity and Skin Effects of Compounds Used in the Rubber and Plastics Industries: II Plasticizers. Arc. Ind. Hyg. Occup. Med. Vol. 2 pp. 231-236, September, 1952.
- 8) Krauskopf, L. G. Studies on the Toxicity of Phthalates via Ingestion. Environ. Health Perspectives. Experimental Issue No. 3 pp. 61-72. January 1973.
- 9) Christensen, H. E., Luginbyl, T. T. Registry of Toxic Effects of Chemical Substances. U. S. Government Printing Office. Washington, D.C. 1975.
- 10) Patty, F. A. Industrial Hygiene and Toxicology; Volume II. Interscience Publishers, John Wiley and Sons Inc. New York, 1967.
- 11) Sax, N. I. Dangerous Properties of Industrial Materials Fourth Edition. Litton Educational Publishing Inc. New York,

TOXICOLOGICAL EVALUATION OF O-DIMETHYL PHTHALATE

February 29, 1976

ABSTRACT

O-Dimethyl phthalate, in studies thus far, has been shown to have a low order of oral and respiratory toxicity. There have been no adverse effects reported with DMP upon the skin either with sensitization or absorption. DMP has a low vapor pressure and is, therefore, not a likely problem in inhalation intoxicification. Orally, DMP has been shown to be toxic only at high dose levels. There have been no carcinogenic or mutagenic effects reported. Teratogenicity has been shown in test animals but only at high dose levels. In view of the present toxicological data available, DMP is suitable for use in solar energy heating and cooling units.

I. Chemical Properties:

Name: o-dimethyl phthalate, phthalate ester.

Molecular formula: $C_6H_4(COOCH_3)_2$

Molecular weight(1): 194.19

Synonyms(1): Avolin; 1,2-benzenedicarboxylic acid, dimethyl ester; dimethyl 1,2-benzenedicarboxylate; dimethyl benzene-orthodicarboxylate; ENT 262; Fermine; methyl phthalate; Mipax; NTM; Dalatinol M; phthalic acid methyl ester; Solvanom; Solvarone.

Melting point (2) and Crystallization points (3): $0.0^{\circ}C$

Boiling point: $540^{\circ}F$

Flash point (2): $325^{\circ}F$

Autoignition point: $1032^{\circ}F$

Specific gravity (2): 1.189

Volatility (4): $> 4 \text{ mg/cm}^3/\text{hr. at } 100^{\circ}C$

Vapor pressure (4): 0.01 mm Hg at $20^{\circ}C$;

12.5 mm Hg at $150^{\circ}C$

Solubility: water (3)(2) $\sim 0.4\%$ ($32^{\circ}C$); 0.5 g/100 ml

ethyl alcohol (5) $\sim$ miscible

ether (5) $\sim$ miscible

benzene (5) $\sim$ soluble

Soluble in most organic solvents and oils (3).

Appearance (3): oily liquid

Color (3)(1): colorless to pale yellow

Odor (3): none or very slight aromatic

Stability (4): Chemically stable except in an alkaline medium which may cause hydrolysis.

II. Hygienic Standards:

TLV: Air 5 mg/m³ (OSHA standard 1910.93)

III. General Toxicity:

Aromatic dicarboxylic acid esters are widely used industrial chemicals most often noted for their use as plasticizers (2). Phthalate esters are prepared from phthalic anhydride and a specific alcohol (6). The majority of the phthalate esters are liquid with high boiling points and low vapor pressures (2). The dicarboxylic acid esters are said to be some of the most inert of all the industrial chemicals used. It has been suggested that the more water soluble a phthalate ester is, the more biologically active it is, and thus the more toxic the compound (7). It has been implicated from research at the cellular level, that phthalate esters with high molecular weights have higher intrinsic toxicities (8). A few phthalate esters, such as DMP, have shown teratogenic characteristics and circumstantial evidence has suggested the possibility of mutagenic effects.

IV. Acute Toxicity:

Although inhalation is not a likely source of entry, due to DMP's low vapor pressure, studies on inhalation have shown adverse effects. A study on cats exposed to 2 mg. of DMP per liter of air resulted in intense irritation of the mucous membranes with salivation and restlessness (3). At 10 mg/l the animals appeared depressed and one died. In the same study

death resulted at a concentration of 9.3 mg DMP per liter of air for 6.3 hours of exposure (2).

Various animal species have been used to test oral acute toxicities. The results range from 2.4 g/kg to 7.2 g/kg and 4.4 ml/kg to 6.9 ml/kg of DMP for a LD₅₀ dose. These results are shown in Table I.

TABLE I

Acute oral toxicity values for DMP.

<u>Animal</u>	<u>LD₅₀ (g/kg)</u>	<u>Reference</u>
mouse	7.2	2
rat	2.4	2
guinea pig	2.4	2
rat	6.9 ml/kg	9
rabbit	4.4 ml/kg	9
chicks	8.5 ml/kg	9

Interperitoneal acute toxicities ranged from 1.58 g/kg to 3.98 g/kg of DMP for a LD₅₀ dose. Table II shows these results.

TABLE II

Interperitoneal acute toxicity values for DMP.

<u>Animal</u>	<u>LD₅₀ (g/kg)</u>	<u>Reference</u>
mouse	3.6	2
mouse	1.58	10
mouse	3.98	11
rat	3.38 ml/kg	7

Irritation response to intradermal injections of DMP in rabbits showed a significant inflammatory response (10). A concentration of the ester was prepared using 100 mg/ml. The rabbits were injected intradermally with 0.2 ml. The degree of extravasation of the indicator dye, after DMP was injected, was marked and showed a rapid and intense concentration at this high dose exposure. In another dermal study using rabbits, the LD₅₀ dose was found to be 10.0 ml/kg (2).

V. Chronic Toxicity:

The chronic toxicity studies involved primarily the effects of DMP when injected. Since this means of exposure is rarely ever encountered outside of the laboratory the results are primarily of academic interest.

Lawrence, et al. (11), injected mice interperitoneally for a three week period. The chronic toxicity value was found to be 1.18 ml/kg for DMP.

Skin sensitization has been reported as showing light to no reaction in guinea pigs (2). The skin LD₅₀ for a rabbit was reported at > 10 ml/kg while a repeated skin application for a 90-day LD₅₀ was reported at > 4 ml/kg with no irritation or sensitization reported.

Studies at the cellular level using DMP application have revealed a variety of results depending on the tissue used. DMP has been shown to be toxic to mouse fibroblasts at high concentrations (8) (10). Inhibition of nervous system tissue outgrowth and degenerative changes to the tissue were observed when DMP was applied to cerebellar tissue from newborn rats (12). The nerve fibers were found to be more sensitive to DMP than the fibroblasts.

The effects of DMP upon fetuses were studied using rats (7). Although high doses (1/3, 1/5 and 1/10 the LD₅₀ dose) of DMP were injected into

pregnant rats with teratogenic effects, it was interesting to note that other phthalate esters did not elicit the same adverse effect. Undiluted phthalate esters were observed to be lethal but not teratogenic to chick embryos in Ovo (13). Chick Ringer's solution saturated with DMP produced teratogenic results when injected into eggs. The most conspicuous effect was the degeneration of extra embryonic blood vessels and growth retardation. The effect of phthalate esters on various explants of embryonic tissue was studied (13). Concentrations of DMP at approximately 0.1-0.5 mg/ml to 1.0 mg/ml for a 8 to 10 hour exposure showed morphological abnormalities. Concentrations of approximately 0.02 mg/ml and lower showed no visible effects.

VI. Human Toxicity:

DMP was first introduced as an insect repellant due to its low skin absorption and toxicity to humans (2). The low vapor pressure of DMP suggests that inhalation of DMP will occur only if introduced as droplets by spraying (14). However, inhalation of DMP may result in irritation of the upper respiratory passages (14). Chronic high dose inhalation may lead to depression of the central nervous system and possible paralysis (3). The results of a study in Russia, where DMP was inhaled at 0.7-1.8 mg/m³, four hours a day for four months, revealed changes in the frequency of respiration and changes in blood morphology as well as in the function of the nervous, hepatic and renal systems (15).

Oral ingestion may cause gastrointestinal irritation with coma and hypotension (2). A dose of 8000 mg/kg is considered a lethal dose (16). Treatment is lavage and catharsis of the victim including artificial respiration if breathing is depressed.

The lack of adverse effects of DMP upon the skin is because it is very poorly absorbed (9), however, some skin absorption has been reported (14). At the highest dose levels employed, mild symptoms of systemic effects were observed. In the previously mentioned Russian inhalation study no irritating effects on the skin were observed (15). No sensitization in humans has been reported (8).

VII. Environmental Toxicology:

Approximately 900 million pounds of phthalate esters are produced a year (8). This exceeds the production of DDT and polychlorinated biphenyls. Not very much is known about phthalate ester occurrence in nature. DMP was found in a perennial Japanese vegetable (8). It is unknown whether DMP was a contaminant of the soil the plant was growing in or whether it was a naturally occurring metabolite of the plant (8). Contamination of the Charles River by DMP and other phthalates was shown to have occurred presumably from industrial wastewater (17). There is some evidence as to the toxic effects of phthalate esters on marine life (8). There have been no studies on the biodegradability of DMP. Other phthalates have been studied for their biodegradability and were found to be comparable to a biodegradable detergent (6).

VIII. Recommendations:

With the continuing use of phthalate esters in industry and commercial products, man's exposure to these chemicals will increase. There is no present information on the accumulation of phthalate esters in the body and at present there appears to be no evidence of phthalate esters as an imminent health threat (8). DMP was shown to be teratogenic but only when injected at high exposure doses. The oral and inhalation results were also observed while employing large dose levels. There have

been no studies showing a carcinogenic or mutagenic effect although mutagenic effects are suspected (8).

As the production of DMP increases, water standards should be set in order to avoid long range pollution problems. The starting base of DMP, phthalate anhydride, is a moderate fire and explosion hazard. Increasing DMP output will also increase the use of phthalate anhydride and its potential as an industrial hazard (8). This potential can be easily controlled and should not be a major concern.

Toxicologically, O-Dimethyl Phthalate appears to be very suitable for use in solar energy heating and cooling units providing a minimum danger to those working with the chemical and those potentially occupying homes which contain DMP in solar energy units.

References

1. National Institute for Occupational Safety and Health. 1975 Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
2. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers, John Wiley and Sons, Inc. New York.
3. Lefaux, René. 1968. Practical Toxicology of Plastics. CRC Press, Chemical Rubber Co., Cleveland, Ohio.
4. National Academy of Sciences. 1959. Handbook of Toxicology. Vol. I, Acute Toxicology, Vol. III, Insecticides.
5. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Co., Cleveland, Ohio.
6. Graham, P. R. 1973. Phthalate Ester - Plasticizers - Why and How they Are Used. Env. Health Perspec. Exp. Issue #3, Jan.:3-12.
7. Singh, A., et al. 1972. Teratogenicity of Phthalate Esters in Rats. J. of Phar. Sci. 61(1):51-55.
8. Autian, John. 1973. Toxicity and Health Threats of Phthalate Esters: Review of the Literature. Env. Health Perspec. Exp. Issue #4. June: 3-26.
9. Draize, John, et al. 1948. Toxicological Investigations of Compounds Proposed for Use as Insect Repellents, J. of Pharm. and Exp. Ther. 93:26.
10. Calley, David, et al. 1966. Toxicology of a Series of Phthalate Esters. J. of Phar. Sci. 55(2):158-162.
11. Lawrence, W. H., et al. 1975. A Toxicological Investigation of Some Acute, Short Term and Chronic Effects of Administering Di-2-Ethyl-hexyl Phthalate (DEHP) and Other Phthalate Esters. Env. Res. 9:1-11.
12. Kasuya, Minoru. 1974. Toxicity of Phthalate Esters to Nervous Tissue in Cultures. Bull. of Env. Cont. and Tox. 12(2):167-172.
13. Lee, Hsin-Yi, et al. 1974. Effects of Phthalate Esters (Plasticizers) on Chick Embryos & Chick Embryonic Cells. Growth 38:301-312.
14. American Conference of Governmental Industrial Hygienists. 1974. Documentation of the Threshold Limit Values. Cincinnati, Ohio.
15. Chemical Abstracts, #107114K Vol. 82. Timofievskaya, L. A., et al., 1974. Experimental Research on the Effect of Phthalate Plasticizers on the Body, (Russia)
16. Dreisbach, Robert. 1974. Handbook of Poisoning, Lange Medical Publications.
17. Hites, Ronald. 1973. Phthalates in the Charles and Merrimack Rivers. Env. Health Perspec. Exp. Issue #3, Jan.:17-21.

TOXICOLOGICAL EVALUATION OF DIETHYL O-PHTHALATE

June 11, 1976

ABSTRACT

Diethyl o-phthalate (DEP) has been shown to have a low order of acute and chronic toxicity. Embryotoxicity and teratogenicity has been demonstrated but only when injected at high dose levels. There have been no carcinogenic or mutagenic effects reported. There is no information at present on body accumulation of DEP. Studies thus far have shown DEP to be an environmental contaminant but with no adverse effects yet reported. In view of the present toxicological data, DEP is recommended for use in solar energy heating and cooling units.

I. Chemical Properties:

Name: Diethyl O-Phthalate (DEP)

Molecular formula: $C_6H_4 (CO_2 C_2H_5)_2$

Molecular weight(1): 222.26

Synonyms(1): ethyl phthalate; Anozol; 1,2-benzenedicarboxylic acid; diethyl ester; diethyl phthalate; Neantine; Palatinol A; Phthalol; Placidol E; Solvanol.

Boiling point: 568°F

Freezing point: -41°F

Vapor pressure(2): 0.05 mm Hg. @ 70°C

Specific gravity: 1.120

Refractive index(3): $n_D = 1.5000$ @ 20°C

Viscosity at stated temperature (centipoises): 4.18 @ 131°F

Solubility(3): water - insoluble; alcohol - soluble; ether - soluble; acetone - soluble; benzene - soluble.

Flash point: 325°F

Appearance(4,5): colorless, oily liquid

Odor: none

II. Hygienic Standard:

TLV: 5 mg/m³ or 0.64 ppm in air as a time weighted average (OSHA standard 1910.93)

III. General Toxicology:

Because of their wide applicability, phthalate acid esters (PAE's) are among the most important of the industrial chemicals (2). Besides their main use as plasticizers, PAE's are also used as defoaming agents in the manufacture of paper, in cosmetics, in lubricating oils and in other industrial and consumer products (6). There is some evidence that PAE's are present as metabolites in certain plants and organisms.

Phthalate esters are prepared from phthalic anhydride and a specific alcohol (7). In general, PAE's are liquid with high boiling points and low vapor pressures (2). The phthalate esters are among the most inert of all the industrial chemicals used and have a low order of toxicity when administered orally (2,8). They are not absorbed by the skin and rarely cause skin problems (2). Because of their low vapor pressure inhalation is not a likely source of entry. There is evidence to indicate teratogenicity of PAE's at high dose levels (9). Mutagenic effects have been suggested for a few of the PAE's. No carcinogenic effects have been reported thus far.

Diethyl phthalate (DEP) is generally regarded as having little acute or chronic toxicity (2,11). DEP is used primarily as a plasticizer of cellulosic materials and has been approved by the FDA for use in food packaging material (2,10). Of all the PAE's, DEP is the one most often used in the perfume industry (6). The TLV of 5 mg/m^3 for this chemical was so recommended because of its low degree of toxicity (11).

IV. Acute Toxicity:

DEP has a low vapor pressure and for that reason inhalation is not a likely problem. However, Patty reports that heated vapors may cause short-term irritation of the nose and throat (2). Rats exposed to 511 ppm

(air through liquid at 150°C) for 6 hours were reported to show vasodilation of ears and feet while cats at 1120 ppm (10 mg/liter mist) for 5 hours were reported to show nasal irritation (2).

Tests done with labeled DEP placed on the skin of rabbits indicate that this particular phthalate ester may pass through the skin more rapidly than previously suspected (6). Intradermal injections of DEP in rabbits showed an irritant response by causing a rapid and intense concentration of extravasated dye at the injected sites (12).

The LD₅₀ for guinea pigs, injected subcutaneously with DEP, was found to be 3.0 g/kg (13). The results of various studies done on the oral toxicity are shown in Table I.

Table 1.
Acute oral toxicity values for DEP.

<u>Animal</u>	<u>LD₅₀ (g/kg)</u>	<u>Reference</u>
rabbit	1.0	13
rat	8.2 (ml/kg)	8
rat	9.5 - 31	10

The available subacute data on oral no-effect levels of DEP taken from FDA studies resulted in a dose of 2,500 mg/kg per day for 6 weeks in the rat and 1,250 mg/kg per day for an unspecified time for dogs (10).

Interperitoneal acute toxicities for various animals are shown in Table II.

Table II.

Acute interperitoneal toxicity values for DEP.

<u>Animal</u>	<u>LD₅₀ (g/kg)</u>	<u>Reference</u>
mouse	2.8	2
mouse	2.83	12
mouse	2.75	13
rat	5.06 (ml/kg)	9

In addition to the above studies, Calley, et al. (12), measured CNS depression following sublethal intraperitoneal injection of DEP. DEP was given as a 500 mg/kg dose and after 30 minutes 60 mg/kg of sodium hexobarbital was injected and the sleeping time measured. The controls had a sleeping time of 46 minutes while the DEP-treated group's time was approximately 88 minutes. These results indicate that DEP at high dose levels is a CNS depressive.

The LD₅₀ intravenous dose for rabbits was reported at 0.1 g/kg and for dogs at 0.28 g/kg (13). Calley, et al. (12), tested respiration rates of rabbits after intravenous injection of various PAE's. After DEP was administered in a total dose of 100 mg/kg, there was a significant increase in the respiratory rate as was also shown with the other phthalate esters tested. In the same study, blood pressure levels were tested. Each dose of 50 mg/kg of DEP administered intravenously caused a 22% transient decrease in the blood pressure level. A total dose of 650 mg/kg was given without lethal or significant effects.

V. Chronic Toxicity:

In a review article by Autian (6), it was stated that even though there was a small amount of chronic toxicity data available on DEP human experience has shown the toxic potential of DEP to be very low. However, irritation of nasal passages and mucous membranes of the upper respiratory tract may occur with prolonged inhalation of its vapors.

The no-effect level of DEP based on chronic feeding studies taken from the FDA files was found to be 1,250 mg/kg of body weight per day for 104 weeks for the rat and for the dog 625 mg/kg of body weight per day for 52 weeks (10).

The embryotoxicity and teratogenicity of various PAE's on rats was studied by Singh, et al. (9). At the 5th, 10th and 15th day of gestation, the phthalate esters were injected interperitoneally at 1/10, 1/5 and 1/3 of the acute LD₅₀ dose of 5.06 ml/kg. After 20 days, the number of corpora lutea, resorption sites, viable and dead fetuses were counted. DEP showed 44.4% resorptions at the low dose level with no gross abnormalities observed but some degree of skeletal abnormalities at all three dose levels was demonstrated. The lower molecular weight PAE's, including DEP, were found to be generally more teratogenic than the higher ones (14). Mutagenic effects have been shown for only a few of the PAE's in preliminary unpublished data with no carcinogenic effects yet demonstrated (6).

The cellular toxicity of PAE's has been studied using mouse fibroblasts (12). DEP was found to be lethal to the cells at 0.05 ml in a 50 mg/ml emulsion. This same dose was not toxic for chick embryo cells. It was found that those phthalate esters more soluble in water were the most toxic.

VI. Human Toxicity:

It has been reported that the action of DEP vapors on the body may cause irritation of the skin and mucous membranes of the nose, throat and eyes (2,5). When absorbed by the skin, DEP is eliminated in the urine as phthalic acid which can be used as a diagnostic test of exposure (4,5). The low vapor pressure of DEP suggests that skin exposure would most likely occur when DEP is in a liquid state in which case there are no major irritant or sensitizing effects on the skin (11). Treatment for exposure to DEP requires irrigation of the eyes with water, washing exposed body areas with soap and water. If ingested, gastric lavage is recommended followed by saline catharsis (4). There are no reports of the possible accumulative effects of DEP in the body (11).

VII. Environmental Toxicology:

There is only limited information on the impact of PAE's on the environment. As of 1973, phthalate ester production was approximately 900×10^6 pounds per year (6). Specifically, DEP is used as a plasticizer, perfume vehicle and in food packaging material (2,10). Known contamination by DEP and other PAE's was found to exist in the Charles River where industrial wastes containing these chemicals were being discharged (15). Currently, there are no restrictions on PAE effluent as a specific water pollutant (6). Other means of environmental contamination by these chemicals include indiscrete disposal of plastics containing these esters. The degree of biodegradability of DEP is not known but other phthalate esters have been studied and were found to be comparable to a biodegradable detergent (7). There is also some evidence as to the toxic effects of PAE's on marine life. In a review article, Autian (6) stated that there

appears to be, at present, no environmental danger but continuing and possibly increasing the use of PAE's may cause long range problems of an unknown nature in the environment.

VIII. Recommendations:

Phthalate acid esters are not considered to be an imminent health threat considering the present information available. The ubiquity of these chemicals supports the need for more environmental research and research concerning the accumulation of phthalate esters in the human body and in ecosystems (6). Acute toxic effects were only noted at high dose levels of DEP or with sources of entry not likely to occur. The limited chronic toxicity information available has shown the toxic potential of DEP to be very low. Teratogenetic effects were reported for DEP only when injected at high dose levels. There have been no studies showing a carcinogenic effect although mutagenic effects are suspected.

Diethyl O-Phthate is recommended for use in solar energy heating and cooling units because of its low toxicity to those working with the chemical and to those occupying homes containing DEP in solar energy units.

References

1. National Institute for Occupational Safety and Health. 1975. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
2. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers, John Wiley and Sons, Inc. New York.
3. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Company. Cleveland, Ohio.
4. Plunkett, E.R. 1966. Handbook of Industrial Toxicology. Chemical Publishing Company.
5. Lefaux, René. 1968. Practical Toxicology of Plastics. CRC Press, Chemical Rubber Company. Cleveland, Ohio.
6. Autian, John. 1973. Toxicity and Health Threats of Phthalate Esters: Review of the literature. Env. Health Perspective, Exp. Issue #4, June: 3-26.
7. Graham, P.R. 1973. Phthalate Ester - Plasticizers - Why and How They are Used. Env. Health Perspective, Exp. Issue #3, Jan.: 3-12.
8. Krauskopf, L.G. 1973. Studies on the Toxicity of Phthalates via Ingestion. Env. Health Perspective, Exp. Issue #3, Jan.: 61-72.
9. Singh, A., et al. 1972. Teratogenicity of Phthalate Esters in Rats. J. of Phar. Sci. 61 (1): 51-55.
10. Shibko, I. and H. Blumenthal. 1973. Toxicology of Phthalic Acid Esters Used in Food - Packaging Material. Env. Health Perspective, Exp. Issue #3, Jan.: 131-138.
11. American Conference of Governmental Industrial Hygienists. 1974. Documentation of the Threshold Limit Values. Cincinnati, Ohio.
12. Calley, David, et al. 1966. Toxicology of a Series of Phthalate Esters. J. of Phar. Sci. 55 (2): 158-162.
13. National Academy of Sciences. 1959. Handbook of Toxicology, Vol. I. Acute Toxicology, Vol. I. Acute Toxicities.
14. Casarett, Louis and John Doull. 1975. Toxicology. Macmillan Publishing Company.
15. Hites, Ronald. 1973. Phthalates in the Charles and Merrimack Rivers. Env. Health Perspective, Exp. Issue #3, Jan.: 17-21.

TOXICOLOGICAL EVALUATION OF PIPERONYL BUTOXIDE

August 25, 1976

ABSTRACT

Piperonyl Butoxide is a methylenedioxyphenyl derivative of piperic acid. It has great industrial importance as a synergist of the pyrethrin insecticides because of its ability to increase the toxicity, persistence, and "knockdown" effect of this class of insecticides. Despite its potent synergistic effect with pyrethrins, piperonyl butoxide is a relatively inert chemical toxicologically. Extensive animal studies and supportive human exposure data indicates that the chemical exhibits a very low order of both acute and chronic toxicity. None of the major routes of exposure give rise to significant physiological syndromes except at extremely large concentrations. In addition, piperonyl butoxide has been shown to have no teratogenic or carcinogenic potential. Although the environmental toxicology of the chemical is not known, it is hypothesized that piperonyl butoxide has little environmental impact. The toxicology of piperonyl butoxide in the industrial environment is also of a very low order with no reported cases of worker intoxication to date.

In view of the toxicological information currently available, piperonyl butoxide is highly recommended as a heat exchange medium for solar heating and cooling.

I. Chemical Properties:

Name: Piperonyl Butoxide

Molecular formula: $C_{19}H_{30}O_5$ (1)

Molecular weight: 338.43 (2)

Synonyms: Toluene, alpha - (2 - (2 - butoxyethoxy) ethoxy) -4,
 5- (methylenedioxy) -2 - propyl-; alpha - (2 - (2-n - butoxyethoxy)
 - ethoxy) - 4, 5 - methylenedioxy - 2 - propyltoluene; (3,4 -
 methylenedioxy - 6 - propylbenzyl) (butyl) diethylene glycol
 ether; 6 - propylpiperonyl butyl diethylene glycol ether; Butyl
 carbitol (6 - propylpiperonyl) ether; Pyrenone 606; Butacide;
 Butocide; Ent 14,250; NIA 5273 (3)

Boiling point: 356°F, 180°C @ 1 mm Hg (2)

Flash point: 340°F

Specific gravity: 1.06

Solubility: Insoluble in water; soluble in petroleum oils,
 dichlorodifluoromethane, alcohol, benzol, Freon, and most
 organic solvents (1,2).

Physical state: Pale, yellow oily liquid, with a faintly bitter
 taste and odorless (1,2)

II. Hygienic Standards:

There are presently no available standards for exposure to piperonyl
 butoxide.

III. General Toxicology:

Piperonyl Butoxide is one of many compounds known as the methylenedioxyphenyl derivatives (4). More specifically, piperonyl butoxide is the methylenedioxy-phenyl derivative of piperic acid (2). First formulated in 1947, piperonyl butoxide is manufactured industrially by the reaction of the chloromethyl derivative of dihydrosafrole with the sodium salt of the mono-n-butyl ether of diethylene glycol (1). To date, piperonyl butoxide has only one use, that being in the formulation of insecticides. Although piperonyl butoxide has some insecticidal properties when used alone, its greatest application is as a synergist when used in tandem with other insecticides. Piperonyl butoxide exhibits its greatest synergistic effect when used in conjunction with the pyrethrins, a class of insecticides that are widely used in commercial home use formulations because of their rapid "knockdown" capabilities (2,5). The use of piperonyl butoxide with pyrethrin allows reduction of concentrations of the insecticide to 10 percent of levels that would be required to obtain the same kill if pyrethrin was used alone. In essence, piperonyl butoxide potentiates the action of the pyrethrins to greatly increase their toxicity, persistence, and "knock-down" effect (2,5). In most formulations, the synergist to insecticide ratio is 8 to 1, with final piperonyl butoxide concentration averaging 0.2 percent by weight (1,6).

The action of piperonyl butoxide in insects that gives it great synergistic potential has been well described. Upon passing into the insect body, piperonyl butoxide becomes a microsomal enzyme inhibitor interfering with detoxification, leading to retention and accumulation of the toxic insecticide or its metabolic derivatives (7). The physiological activity of piperonyl butoxide has been accredited to the presence of the methylenedioxy group in its chemical structure (2).

In general, the toxicity of piperonyl butoxide is considered to be of an extremely low order. When tested alone, the chemical is essentially nontoxic to higher animals and man, although it possesses mediocre insecticidal power (2). It appears that piperonyl butoxide does not present significant health hazards from acute or chronic exposure, with no route of exposure exhibiting a high affinity for toxicological response.

IV. Acute Toxicity:

The bulk of available information on the acute toxicity of piperonyl butoxide comes from a study conducted by Sarles, et al. (6). In this study, a variety of experimental animals were administered doses of piperonyl butoxide orally and dermally, in an attempt to access the acute toxic potential of the chemical. The LD₅₀ values generated from this study, plus additional acute toxicity data on piperonyl butoxide, are summarized in Table I.

Table I.

Acute Toxicity Data for Piperonyl Butoxide

<u>Route of Exposure</u>	<u>Animal</u>	<u>LD₅₀</u>	<u>Reference</u>
Oral	Rat	7.5 - 10.0 ml/kg	6
	Rat	11.5 ml/kg	8
	Rat	11,500 ml/kg	2
	Mouse	8.3 ml/kg	8
	Mouse	3.8 ml/kg	2
	Rabbit	2.5 - 5.0 ml/kg	6
	Rabbit	7,500 mg/kg	3
	Cat	>10 ml/kg	6
	Dog	>7.5 ml/kg	6

<u>Route of Exposure</u>	<u>Animal</u>	<u>LD₅₀</u>	<u>Reference</u>
Dermal	Rabbit	>1,800 mg/kg	2
Subcutaneous	Rat	>15.0 ml/kg	6
Intraperitoneal	Mouse	1,000 mg/kg	3

As evidenced by the extremely large LD₅₀ values on experimental animals, the acute toxicity of piperonyl butoxide from the oral and dermal routes of exposure is of a very low order. In addition to this, Sarles (6) states that the danger of delivering an acutely toxic dose of piperonyl butoxide via the respiratory tract is negligent, since the chemical was relatively nontoxic when introduced directly into the tissues by subcutaneous injection. When systemic illness was induced in animals by large doses of piperonyl butoxide, it was characterized by passage of black feces, bloody discharge from eyes and nose, weakness, loss of appetite, and loss of weight. However, all animals were completely recovered within one week and no signs of gross pathology were found in the survivors (6).

The ability of piperonyl butoxide to cause primary irritation of the eyes and skin has also been tested in animals. Undiluted piperonyl butoxide, in amounts of one-tenth milliliter, produced very little if any irritation in the eyes of rabbits, cats, and dogs. In rabbits, the chemical causes only a mild and transient irritation that completely clears in 48 hours. In cats and dogs, piperonyl butoxide is considered completely nonirritating to the eye (6). The potential of the chemical to irritate intact skin is essentially of the same order. Piperonyl butoxide applied to the clipped skin of rabbits, produces only a barely perceptible edema and reddening of the skin that completely clears in 72 hours (6). In addition, dermal absorption of the chemical is poor and no

sensitization has been seen in rabbits when repeatedly exposed to piperonyl butoxide dermally (6).

In conclusion, the ability of piperonyl butoxide to be acutely toxic is negligible. The large doses required to induce systemic illness and death in experimental animals, indicate that acute intoxication in humans would be nearly impossible from any route of exposure. In addition, the ability of the chemical to damage the eye, or potentiate a dermatitis can only be considered to be slight.

V. Chronic Toxicity:

The chronic toxicity of piperonyl butoxide, like its acute toxicity, is of a very low order. All available data indicates that piperonyl butoxide can be tolerated in large proportions on a daily basis without adverse effect. Again, the bulk of the toxicological information has been generated by Sarles, et al. (9). In 1952, they carried out an extensive study on the chronic oral toxicity of piperonyl butoxide in rats, dogs, goats, and monkeys. They found the chemical to have a relatively low order of oral toxicity for the warm blooded animals tested, with little difference between species. The bulk of the research was done on rats and dogs with the following results. Rats fed daily diets, with graded dosages of piperonyl butoxide over a two year period, exhibited a marked tolerance to the chemical. One hundred ppm proved nontoxic, 1000 ppm were tolerated in good health, 10,000 ppm revealed a moderate toxicity characterized by anorexia, wasting, reduced food consumption, and accentuation of concomitant natural disease, while 25,000 ppm were fatal in 4 to 68 weeks. A similar study with dogs spanning a one year time period, produced similar results. At 80ppm, piperonyl butoxide was non-toxic, 700 ppm were tolerated in good health, 3000 ppm were moderately

toxic producing a symptomology similar to that for rats, and 11,000 ppm were fatal within 4 to 15 weeks (9).

In addition to these findings which indicate that the chronic oral toxicity of piperonyl butoxide is of a very low order, Sarles, et al. (9) arrived at a series of conclusions about the cumulative effects of the chemical. First, it was shown that ingested doses of piperonyl butoxide are quickly eliminated from the body via the feces, and to a lesser degree in the urine. This finding was upheld when no cumulative effects were found in the second and third generations of rats fed daily diets including up to 10,000 ppm piperonyl butoxide. Secondly, it was concluded that piperonyl butoxide was not teratogenic since all animal species reproduced normally during and after the long term exposure to the chemical. Finally, there was no evidence found to indicate that piperonyl butoxide may have carcinogenic potential. No malignant tumors were found in the general tissues, liver, endocrine glands, or breasts of any test animal.

Sarles, et al. (6) are also the sources of data for chronic dermal and respiratory exposure to piperonyl butoxide. Nine doses of undiluted piperonyl butoxide, each being 0.25 ml, were applied to the skin of rabbits over a two week period. A dermatitis characterized by definite thickening and reddening of the skin, and roughening, thickening, and cracking of the epidermis resulted but started to subside two weeks after the last exposure. Although the undiluted solution exhibited a moderate dermal reaction, a four percent water emulsion of piperonyl butoxide was completely nonirritating. The effects of chronic respiratory exposure to piperonyl butoxide in rats has also been explored. Rats were exposed to heavy concentrations of insecticidal sprays and aerosols containing piperonyl butoxide for 30 minutes a day for 24 days. None of the rats

showed any signs of intoxication during or after the 24 day exposure period. These results for chronic dermal and respiratory exposure to piperonyl butoxide, support the low order of toxicity found for the chemical in the long term ingestion studies previously cited.

In an attempt to relate the findings of their exhaustive animal studies to humans, Sarles, et al. (9) estimated that an average daily intake of 42 ppm in the diet could be tolerated by humans without adverse effect. This figure is based on their animal data plus the incorporation of a 100-fold safety factor, and is still considered valid today. However, in recent years there has been some question over the toxic potential of piperonyl butoxide for humans from chronic exposure. Although shown to not have a cumulative or carcinogenic effect in animals, there has been some speculation that piperonyl butoxide may show some degree of persistence in the human body. The chemical alone is not a suspect human carcinogen, but accumulated amounts in the body may inhibit the enzymatic detoxification of other potent carcinogenic organic compounds present in the environment (7). Conney, et al. (4) tested this theory in experimental animals and man in 1972. They found that a dose of piperonyl butoxide, 50 times greater than the daily exposure of most humans, was required before *in vivo* metabolic detoxification of chemicals, hormones, and pharmaceuticals was adversely affected. On the basis of this finding, they rejected the hypothesis that piperonyl butoxide played a role in the pathogenesis of human cancer.

In conclusion, the chronic toxicity of piperonyl butoxide is of a very low order. Exhaustive animal data, plus some supporting human evidence shows the chemical to be almost toxicologically inert at concentrations that humans would normally be exposed to over long periods of time.

VI. Environmental Toxicology:

The action of piperonyl butoxide in the environment is not known. Although the chemical might be expected to show some environmental persistence since it enhances the persistence of the pyrethrin insecticides for which it is a synergist, this could not be supported by current literature. In addition, no information could be found that assessed the ability of piperonyl butoxide to biomagnify in the food chain. However, the fact that the chemical does not have an accumulative effect in experimental animals or humans, may suggest that biomagnification in lower species would not occur.

Very little information is also available on the toxicology of piperonyl butoxide in the industrial environment. To date, there have been no reports of intoxication in workers involved in the manufacture of the chemical, or in formulation of insecticides. This most likely can be attributed to the fact that piperonyl butoxide is one of the safest and least toxic compounds used in insecticides (6).

VII. Recommendations:

On the basis of toxicological information currently available, piperonyl butoxide is highly recommended for use as a heat exchange medium for solar heating and cooling. Extensive animal studies, and supportive human data indicate that piperonyl butoxide exhibits a very low order of both acute and chronic toxicity. None of the major routes of exposure give use to significant physiological syndromes, except at highly inflated concentrations that in themselves are unrealistic. In addition, the hypothesis that piperonyl butoxide may have very little environmental impact, coupled with its low order of industrial toxicity,

make the chemical a favorable toxicological choice as a heat exchange medium in a system that may find wide private and commercial use.

References

1. Martin, Hubert. Guide to the Chemicals Used in Crop Production. Second Edition. Canada Department of Agriculture. 1953.
2. Negherbon, W.O. Handbook of Toxicology. Volume III: Insecticides. W.B. Saunders Company. Philadelphia. 1959.
3. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
4. Conney, A.H., et al. Effects of Piperonyl Butoxide on Drug Metabolism in Rodents and Man. Archives of Environmental Health. Vol. 24. pp. 97-106. February, 1972.
5. Hamilton, A. and H.L. Hardy. Industrial Toxicology. Publishing Science Group, INC. Acton, Massachusetts. 1974.
6. Salres, M.P. Acute Toxicity and Irritation Tests on Animals With the New Insecticide, Piperonyl Butoxide. American Journal of Tropical Medicine. Vol. 29. pp. 151-167. 1949.
7. Falk, H.L., et al. Carcinogenic Potential of Pesticides. Archives of Environmental Health. Vol. 10. pp. 847-858. 1965.
8. Draize, J.H., et al. Toxicological Investigations of Compounds Proposed For Use as Insect Repellents. Journal of Pharmacology and Experimental Therapeutics. Vol. 93. pp. 26-39. 1948.
9. Sarles, M.P. and W.B. Vandergrift. Chronic Oral Toxicity and Related Studies on Animals With the Insecticide and Pyrethrum Synergist, Piperonyl Butoxide. American Journal of Tropical Medicine and Hygiene. Vol. 1. pp. 862-883. 1952.

TOXICOLOGICAL EVALUATION OF DI (2-ETHYLHEXYL) ADIPATE

August 26, 1976

ABSTRACT

Di (2-Ethylhexyl) Adipate (DEHA) is one of several esters of adipic acid. It has found wide use in industry as a plasticizer because of its ability to impart flexibility and resistance to plastics that are to be used at cold temperatures. The toxicology of DEHA is of an extremely low order. Tests on experimental animals have shown that DEHA only exhibits a toxic action at extremely high concentrations for both acute and chronic exposures. The only physiological effect caused by exposure to DEHA is its ability to cause slight irritation of the eyes, skin, and respiratory tract. The nontoxic nature of DEHA is caused by poor absorption of the chemical by the body regardless of route of exposure. In addition to its low order of toxicity, DEHA does not accumulate in the body and has been proven to be noncarcinogenic in experimental animals. The industrial toxicology of the chemical parallels those for acute and chronic exposure. The only toxicological drawback of DEHA may be its ability to show some environmental persistence, however, this is not conclusively proven.

On the basis of toxicological information currently available, DEHA is recommended for use as a heat exchange medium for solar heating and cooling.

I. Chemical Properties:

Name: Di (2-Ethylhexyl) Adipate (DEHA)

Molecular formula (1): $C_{22}H_{42}O_4$

Molecular weight (2): 370.58

Synonyms (1,3): Bis (2-ethylehexyl) adipate; Hexanedioic acid, di (2-ethylhexyl) ester; Hexanedioic acid, bis (2-ethylhexyl) ester; Dioctyl adipate; Monoplex DOA; Bisoflex DOA; Truflex DOA; Adipol 2EH; DOA

Freezing point (2): -76°F Boiling point (1): 782°F , 218°C @ 4 mm HgFlash point: 385°F

Specific gravity: 0.9268

Viscosity: 13.7 centipoises @ 68°F Refractive index (2): $N_D = 1.4474$ @ 20°C

Solubility (1,2): Insoluble in water and glycerine; soluble in alcohol, ether, acetone, and acetic acid

Physical state (1): Colorless or very pale amber liquid, with a slight aromatic smell

II. Hygienic Standards:

There are presently no available standards for exposure to di (2-ethylhexyl) adipate.

III. General Toxicology:

Di (2-ethylhexyl) Adipate (DEHA) is one of several esters of adipic acid. Like all aliphatic esters, DEHA is formed by replacing the hydrogen of adipic acid with an organic grouping in a process known as esterification (4). Aliphatic esters in general, and DEHA in particular have gained industrial importance as plasticizers. DEHA has wide application in the plastics industry because of its ability to impart flexibility and resistance to plastics that are normally used at cold temperatures (1). DEHA is the plasticizer of choice for use with vinyl resins when finished products are intended for use at lower temperatures. In addition, DEHA is an excellent plasticizer for synthetic rubber, nitrocellulose, and ethyl cellulose (1).

In general, practically all of the aliphatic esters used as plasticizers are toxicologically inert (4). The most common physiological effect of these compounds is slight irritation of the respiratory membranes and skin upon prolonged exposure to heated vapor of the esters. Although sensitization to the aliphatic ester plasticizers has been reported, continuing experience indicates it to be a very rare occurrence and possibly due to impurities or decomposition products present in the esters (4). The esters of adipic acid exhibit a toxicology almost identical to the rest of the aliphatic ester plasticizers. They all show a low degree of acute and chronic toxicity, with slight irritation of the eye, skin, and respiratory tract. These effects appear to be the only toxic responses from exposure to the adipic acid esters. Although specific information concerning the toxic potential of DEHA is sparse, that which is available indicates that this ester exhibits the low order of toxicity typical of other aliphatic acid esters.

IV. Acute Toxicity:

All of the information currently available on the acute toxicity of DEHA is unpublished data cited by Patty (4) and Lefaux (1). However, at least some information on the acute response is available for all major routes of exposure. The LD₅₀ values for DEHA generated in experimental animals are summarized in Table I.

Table I.

LD₅₀ values for Di (2-Ethylhexyl) Adipate

<u>Route of Exposure</u>	<u>Animal</u>	<u>LD₅₀</u>	<u>Reference</u>
Oral	Guinea Pig	14 ml/kg	1
	Rat	9.11 ml/kg	1
	Rat	9.1 g/kg	4
	Rat	20-50 g/kg	4
Intraperitoneal	Rat	>47 g/kg	4
	Mouse	150 g/kg	4
Dermal	Rabbit	16.3 ml/kg	4

The LD₅₀ values indicate that the acute toxicity of DEHA is of an extremely low order, almost to the point of being insignificant. Lefaux (1) states that the effects of acute intoxication of DEHA are not immediately apparent. Experimental animals exposed to LD₅₀ concentrations of the chemical show little physiological change for three days following exposure. Only after this lag period will signs of intoxication be seen, and fatality may take weeks. The extremely large LD₅₀ values and lag period following exposure are due to poor absorption of DEHA *in vivo*. Intoxicated animals produce an oily stool, indicating that absorption of the chemical by the

gastrointestinal tract is slow and incomplete (4). Skin absorption of DEHA is also insignificant as evidenced by the high LD₅₀ value for dermal exposure.

The acute toxic effects of inhalation of DEHA vapor are also slight in magnitude. Rats exposed to air saturated with DEHA vapor for periods of up to 8 hours experienced no mortality and only slight respiratory irritation (4). The irritating effect of the chemical on the skin and eyes of guinea pigs is equally as slight.

In conclusion, the acute toxic potential of DEHA is of an extremely low order. The physiological effects of intoxication with DEHA through any route of exposure are insignificant, except at extremely inflated concentrations that would never occur under normal conditions.

V. Chronic Toxicity:

The effects of chronic exposure to DEHA are as minimal as those from acute exposure. Although no information is available on the chronic effects of respiratory exposure, data collected from long term oral and dermal studies with experimental animals indicates that DEHA is rather innocuous. In studies performed with rats, daily diets containing 100 mg DEHA/kg had no physiological effect when ingested over a 19 month period. The rats show no signs of disturbance in growth, reproduction, or histopathology. Only when concentrations of DEHA reached 5 percent of the daily diet was there a definite growth effect, and 4.74 g/kg had to be ingested daily for several weeks before death could be induced (1,4). Results in dogs are comparable to those in rats. Dogs exposed orally to 2 g DEHA/kg over a two month period exhibited only transient loss in appetite, with no changes in the blood, urine, or weight of liver and kidney (4).

The carcinogenic potential of DEHA has been assessed for oral and dermal exposures in separate studies in France and the United States. A French study, cited by Lefaux (1) tested the ability of DEHA to cause cancer from chronic oral exposure. Rats, orally exposed to daily dosages of 100 mg/kg, were free of tumor production after one year and seven months of continual exposure. Tests to determine the power of DEHA to potentiate skin cancer in mice produced similar results. Mice injected with a single, subcutaneous dose of 10 mg failed to produce skin tumors in their span of up to 575 days. In addition, doses of 10 mg applied once a week to the shaven skin of mice, also produced no evidence of tumors in life spans of up to 459 days (5).

In conclusion, the chronic toxicity of DEHA is of a low order. From the information available at this time, it would appear that DEHA does not have a cumulative effect in the body, and that long term exposure to relatively high doses of the chemical produces little physiological damage. Both of these assumptions are supported by the fact that DEHA is not efficiently absorbed by the body, regardless of route of exposure.

VI. Environmental Toxicology:

The action of DEHA on the environment is not known. To date, no reports on the chemicals biodegradability, nor its ability to biomagnify in the food chain, could be found in the literature. Although other esters used as plasticizers have shown some persistence in the environment and ability to accumulate in the food chain, DEHA has not yet been implicated as an environmental pollutant.

The toxicology of DEHA in the industrial environment, is of a low order. No reports of worker intoxication from acute or chronic exposure

to DEHA have arisen in its many year history in plastics formulation. However, caution should be used when DEHA is heated to a temperature of vaporization, or when plastics containing DEHA are heated to temperatures of 222°C or more. Workers involved in the meat cutting and sealing processes used to wrap meat have experienced lung, throat, and eye irritation when the plastic film in use releases DEHA vapors upon heating of the film to 200°C (6). However, the irritant action of DEHA is not considered a major health threat and can easily be controlled with adequate ventilation of the workplace.

VII. Recommendations:

In view of the toxicological information currently available, DEHA is recommended as a heat transfer medium for solar heating and cooling. The chemical shows an extremely low order of toxicity from both acute and chronic exposure in animals, and significant intoxication in humans has not been reported. In addition, DEHA is not accumulated in the body because of poor absorption and the chemical has been proven to have no carcinogenic potential in experimental animals. The chemical's only toxic effect of significance at lower concentrations is its ability to cause slight irritation of the eyes, skin, and respiratory tract. For all practical purposes, DEHA can be considered to be toxicologically inert, and hence a good choice as a heat exchange medium in a solar energy system that may find widespread public use.

REFERENCES

1. Lefaux, René. Practical Toxicology of Plastics. Iliffe Books Ltd. London, England. 1968.
2. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
3. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
4. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
5. Hodge, H.C., et al. Tests on Mice for Evaluating Carcinogenicity. Toxicology and Applied Pharmacology. Vol. 9. pp. 583-596. 1966.
6. Jaeger, R.J., and R.A. Hites. Pyrolytic Evaporation of a Plasticizer from Polyvinyl Chloride Meat Wrapping Film. Bulletin of Environmental Contamination and Toxicology. Vol. II. pp. 45-48. 1974.

TOXICOLOGICAL EVALUATION OF DI (2-ETHYLHEXYL) SEBACATE

September 3, 1976

ABSTRACT

Di (2-Ethylhexyl) Sebacate, more commonly referred to as dioctyl sebacate (DOS), is an aliphatic ester of sebacic acid. It has found rather extensive use as a plasticizer because of its ability to impart flexibility to plastics intended for use at low temperatures. In general, aliphatic acid esters used as plasticizers are toxicologically inert. The sebacates and DOS display such a toxicology. Although specific information on the toxic potential of DOS is sparse, the acute and chronic studies that have been carried out show DOS to produce little, if any, physiological effect in animals and man. It is not a dermal or respiratory irritant nor a carcinogen, and sensitization to DOS is extremely rare. The environmental toxicology of DOS is not known, but it should be pointed out that some esters used as plasticizers have shown some environmental persistence. In the industrial environment, DOS has been widely used with no reports of worker intoxication.

In view of toxicological information currently available, Di (2-Ethylhexyl) Sebacate is recommended for use as a heat exchange medium for solar heating and cooling units.

I. Chemical Properties:

Name: Di (2-Ethylhexyl) Sebacate

Molecular formula (1): $(\text{CH}_2)_8 (\text{CO}_2\text{C}_8\text{H}_{17})_2$

Molecular weight (2): 426.69

Synonyms (3): Bis (2-Ethylhexyl) Sebacate
Decanedioic Acid, Bis (2-Ethylhexyl) ester
Dioctyl Sebacate
1-Hexanol, 2-Ethyl-, Sebacate
2-Ethylhexyl Sebacate
Octyl Sebacate
Monoplex DOS
Bisoflex DOS
Stafllex DOS
Octoil S
Px 438
DOS

Freezing point: -67°F Boiling point (2,1): 256°C , 248°C @ 4 mm HgFlash point: 410°F

Specific gravity: 0.913

Refractive index (2): $N_D = 1.451$ @ 25°C

Solubility (1): 0.02% in water @ 20°C ; soluble in hydrocarbons,
alcohols, ketones, esters, and chlorinated solvents; insoluble
in glycols.

Physical state (1): Odorless, colorless, oily liquid

II. Hygienic Standards:

There are presently no available standards for exposure to di (2-ethylhexyl) sebacate.

III. Toxicology:

Di (2-Ethylhexyl) Sebacate, more commonly known as dioctyl sebacate (DOS), is an ester of sebacic acid. Like other esters, DOS is formed by a process known as esterification, where the hydrogen of an acid is replaced by an organic grouping (4). The esters of sebacic acid have found wide industrial use as plasticizers. Fourteen sebacates are currently used in the plastics industry, with dibutyl sebacate and DOS by far being the most popular. DOS has gained primary importance as a plasticizer because of its ability to impart elasticity to plastics over a wide temperature range. Its most significant application is in plastics that are intended for use at low temperatures, but must remain flexible. DOS is considered to be the best low temperature plasticizer commercially available for polyvinyl chloride and polyvinyl chloride-acetate. In addition, it is also compatible with nitrocellulose, ethyl cellulose, and polyvinylidene chloride, and is an excellent plasticizer for elastomers (1). Although its primary industrial use is as a plasticizer. DOS is also used as a synthetic lubricant for reaction motors because of its ability to remain stable over a wide range in temperature.

In general, the toxicology of esters can be correlated fairly well with their chemical structures. With few exceptions, the common aliphatic esters used as plasticizers are toxicologically inert (4). The sebacates are included in this group of esters. At the most, minor degrees of irritation may follow inhalation of heated vapor or extensive, prolonged dermal exposure. Although sensitization has been reported, it is a very rare occurrence and may possibly be due to impurities in the ester or decomposition products. Although actual data is not available, the lack of toxic potential in the sebacates is believed to be due to lack of absorption by

the body, or conversion of the esters by hydrolysis to normal metabolites or to materials readily excreted in the urine (4).

Although little toxicological information is currently available as proof, the toxicology of DOS seems to match that of the other sebacates. The only acute toxicity data on DOS that could be found is unpublished data of the Eastman Kodak Company cited by Patty (4). The LD₅₀ values obtained in this study are summarized in Table I. In addition to this data,

Table I.

Acute Toxicity Data for Di (2-Ethylhexyl) Sebacate

<u>Route of Exposure</u>	<u>Animal</u>	<u>LD₅₀</u>
Oral	Rat	12.8 - 25.6 gm/kg
	Mouse	12.8 - 25.6 g/kg
Intraperitoneal	Rat	>25.0 gm/kg
	Mouse	>25.0 gm/kg
Dermal	Guinea Pig	>10.0 ml/kg

the effects of inhalation of DOS, and its irritant properties were also evaluated. Rats submitted to atmospheres saturated with DOS vapor for six hour periods exhibited no mortality or respiratory irritation. In addition, DOS applied to the intact skin of guinea pigs did not produce an irritant effect of any kind, nor was it absorbed through the skin. The results of the Eastman Kodak study tend to indicate that the toxic potential of DOS from acute exposure is negligible. Acute exposure via any of the major routes produces little, if any, physiological effect.

The effects of chronic exposure to DOS are seemingly as negligible as those from acute exposure. Again only one study assessing the chronic

toxic potential of DOS could be found. A nineteen month toxicity test was carried out by the French Centre for research on the Normal and Cancerous Cell and is cited by Lefaux (1). In this study, rats were fed daily diets containing 200 mg/kg DOS. The results support the hypothesis that DOS is toxicologically inert. Growth patterns of the test animals were not disturbed. Reproduction and growth in subsequent generations of rats were also unaffected. During the nineteen months, no pathological symptoms were observed in the animals, and macroscopic and microscopic examination of internal organs at the end of the investigation period failed to reveal any lesions or abnormalities. In addition, it was concluded that DOS has no carcinogenic potential.

The environmental toxicology of DOS is not known. To date no studies have been carried out to assess the biodegradability of the chemical. It should be pointed out, however, that some of the esters used as plasticizers have shown some environmental persistence and the sebacates may be included in this group. In the industrial environment, DOS is generally regarded to be toxicologically inert. There have been no reports of worker intoxication due to exposure to DOS. However, any industrial chemical should be handled properly and with care to avoid excessive exposure.

IV. Recommendations:

On the basis of toxicological information currently available, Di (2-Ethylhexyl) Sebacate is recommended for use as a heat exchange medium for solar heating and cooling. Although little data has been generated to date, the acute and chronic studies that have been carried out indicate that DOS is toxicologically inert. The physiological effects produced by exposure to DOS from any major route are minimal, if present at all. In

addition, DOS has been shown to be noncarcinogenic and can be safely handled in an industrial environment with a minimum of caution.

References

1. Lefaux, René. Practical Toxicology of Plastics. Iliffe Books Ltd. London, England. 1968.
2. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
3. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
4. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.

TOXICOLOGICAL EVALUATION OF DIBUTYL SEBACATE

September 9, 1976

ABSTRACT

Dibutyl sebacate (DBS) is an ester of sebacic acid. It has found rather extensive use as a plasticizer because of its ability to impart flexibility to plastics intended for use at lower temperatures. In general, aliphatic acid esters used as plasticizers are toxicologically inert. The sebacates and DBS display such a toxicology. Although specific information on the toxic potential of DBS is sparse, the one study that has been carried out showed the chemical to cause only minor exposure. No data is currently available that assesses the ability of DBS to be toxic from respiratory or dermal contact, but all indications are that the hazard would be insignificant. The environmental toxicology of DBS is not known, but it should be pointed out that some esters used as plasticizers have shown some environmental persistence. In the industrial environment, DBS has been widely used with no reports of worker intoxication.

In view of toxicological information currently available, dibutyl sebacate is recommended for use as a heat exchange medium for solar heating and cooling.

I. Chemical Properties:

Name: dibutyl sebacate

Molecular formula (1): $[(CH_2)_4 COO C_4H_9]_2$

Molecular weight (1): 314.47

Synonym: DBS

Freezing point (1): 12°F

Boiling point (1): 660°F

Flash point: 350°F

Specific gravity (1): 0.9405

Refractive index (1): $N_D = 1.4433$ @ 15°C

Solubility (1): insoluble in water; soluble in ether

Physical state (2): pale yellow liquid

II. Hygienic Standards:

There are presently no available standards for exposure to dibutyl sebacate.

III. Toxicology:

Dibutyl sebacate (DBS) is one of many esters of sebacic acid. Like other esters, DBS is formed by a process known as esterification, where the hydrogen of an acid is replaced by an organic grouping (3). The esters of sebacic acid have found wide industrial use as plasticizers. Fourteen sebacates are currently used in the plastic industry, with DBS by far being the most popular. DBS has gained primary importance as a plasticizer

because of its ability to impart elasticity to plastics over a wide temperature range. Its most significant application is in plastics that are intended for use at low temperatures. DBS is an excellent plasticizer for polyvinyl chloride, and is considered the plasticizer of choice for cellulose acetobutyrate, polyvinyl butyral, rubber hydrochloride, and polyvinylidene chloride. In addition, it is equally compatible with nitrocellulose, ethyl cellulose, polystyrene, and many synthetic rubbers (2).

In general, the toxicology of esters can be correlated fairly well with their chemical structures. With few exceptions, the common aliphatic esters used as plasticizers are toxicologically inert (3). The sebacates are included in this group of esters. At the most, minor degrees of irritation may follow inhalation of heated vapor or extensive, prolonged dermal exposure. Although sensitization has been reported, it is a very rare occurrence and may possibly be due to impurities in the ester or decomposition products. Although actual data is not available, the lack of toxic potential in the sebacates is believed to be due to lack of absorption of the body, or conversion of the esters by hydrolysis to normal metabolites or to materials readily excreted in the urine (3).

Although little toxicological information is currently available as proof, the toxicology of DBS seems to match that of the other sebacates. To date only one comprehensive toxicological study has been done on DBS, that being a 1953 investigation cited by Lefaux (2). This study tested the acute and chronic toxicological potential of DBS on the white rat via oral administration. The acute oral toxicity of DBS was tested by administering doses ranging from 1 to 32 g DBS per kg body weight to male rats weighing 60 to 75 g. All doses up to 16 g/kg were tolerated by the rats without physiological effect. The oral LD₅₀ of DBS in rats was determined

to be in the range of 16 to 32 g/kg. The chronic oral toxicity of DBS was tested by administering varying doses of the chemical in the daily diet of rats for a 24 month period. DBS concentrations ranged from 0.01 to 6.25 percent of the daily food intake for five groups of rats, with two additional groups acting as controls. At the two highest concentrations, 6.25 and 1.25 percent, DBS had no effect on growth or the blood forming tissues. In addition, no mortality was seen and there was no effect on reproductive capabilities. The only physiological effect noted that could be attributed to consumption of DBS, was a slight action on the growth of second generation animals. Although the study did not test the toxic potential from oral administration plus the fact that the sebacates as a group are considered toxicologically inert, would tend to indicate that these routes of exposure can be virtually disregarded.

The environmental toxicology of DBS is not known. To date, no studies have been carried out to assess the biodegradability of the chemical. It should be pointed out, however, that some of the esters used as plasticizers have shown some environmental persistence, and the sebacates may be included in this group. In the industrial environment, DBS is generally regarded to be toxicologically inactive. There have been no reports of worker intoxication due to exposure to DBS. However, any industrial chemical should be handled properly and with care to avoid excessive exposure.

IV. Recommendations:

On the basis of toxicological information currently available, dibutyl sebacate is recommended for use as a heat exchange medium for solar heating and cooling. Although little data has been generated to date, the one stud

that has been performed indicates that DBS is capable of only insignificant oral intoxication from either acute or chronic exposure. In addition, DBS is not expected to cause major physiological changes if exposure is from skin contact or inhalation. Finally, DBS is most likely not a major environmental pollutant and can be handled in an industrial setting with a minimum of caution.

References

1. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
2. Lefaux, René. Practical Toxicology of Plastics. Iliffe Books Ltd. London, England. 1968.
3. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers. John Wiley and Sons, Inc. New York. 1967.

TOXICOLOGICAL EVALUATION OF PETROLATUM

August 30, 1976

ABSTRACT

Petrolatum is a purified mixture of semisolid hydrocarbons obtained from petroleum. This compound has numerous applications in the cosmetic, drug and food industry. Little is known of its acute or environmental toxicity. Exposure to the vapors of petrolatum may cause aspiration pneumonia but the high boiling point of petrolatum makes this exposure route unlikely. Studies have primarily centered on petrolatum's chronic effects. Data on oral, subcutaneous and topical exposure have shown this compound to be of a low order of toxicity. Based on the data available, petrolatum is recommended for use in solar energy heating and cooling units.

I. Chemical Properties:

Name: petrolatum, liquid

Molecular formula (1): a purified mixture of semisolid hydrocarbons obtained from petroleum.

Molecular weight: varies with purity

Synonyms: white mineral oil; paraffin oil

Boiling point: varies with purity

Specific gravity (1): between 0.815 and 0.880 @ 60°C

Flash point: 444°F

Solubility (1): water - insoluble; alcohol - slightly soluble; ether, benzene, carbon disulfide, chloroform, turpentine oil, solvent hexane - soluble

Odor: none

Appearance (1): an oily liquid from white to light amber in color depending on purity

II. Hygienic Standards:

Although there is no specific hygienic standard for petrolatum, a closely related compound, paraffin wax, has a TLV of 2 mg/m³. (OSHA standard 1910.93).

III. General Toxicity:

Petrolatum is an unctuous purified mixture of semisolid hydrocarbons obtained from a paraffin base and a mixed base crude oil (1,2). After dewaxing, the crude petrolatum is then subjected to a refining process to remove odor, taste and decolorize it according to specifications of the National Formulary or U.S. Pharmacopeia (2).

Petrolatum has had numerous applications through the years in the cosmetic, drug and food industry (1). Cosmetically and medicinally, it has been used in ointments, creams and other preparations. In the food industry it has been used as a defoaming agent, protective coating, lubricant and release agent (1). There is no documented use of petrolatum as an industrial chemical.

Because of its diverse chemical makeup, petrolatum does not belong to any specific family of compounds, although it is closely related to the paraffin waxes and can be defined as a soft-type microcrystalline wax (2). The toxicology of the paraffin waxes has been extensively studied because of the widespread use of these compounds in food packaging (3). Polycyclic aromatic hydrocarbons have sometimes been shown to be components of petrolatum and paraffin waxes depending on the purity of the compound in question (2,3). Many of these hydrocarbons have been reported to be carcinogenic. Studies have, therefore, centered around the potential carcinogenicity of these compounds when ingested, applied topically or injected subcutaneously. In general, the results have shown petrolatum to be relatively nontoxic and absent of any carcinogenic activity (2,3,4).

IV. Acute Toxicity:

There is little available literature on the acute effects of petrolatum. From the chronic toxicity data available, this compound appears to be innocuous at those dose levels for which humans are subjected to in food, cosmetic and drug preparations (2,3,4). Although inhalation is not a likely route of exposure, Sax (7) states that vapors of this compound may cause aspiration pneumonia. Caution should therefore be taken when dealing with petrolatum in a manner that may produce an aerosol or vapor.

V. Chronic Toxicity:

Studies concerning petrolatum have centered on its chronic effects through various routes of exposure. Analysis of the components of the compound was performed for each study. The components were found to vary depending on the source and purity of each sample tested.

Oser, et al. (2) fed rats a diet consisting of 5 percent of one of three petrolatum blends for a period of 2 years. The body weights were observed as well as the effect of the compound upon the metabolism and the internal organs of the animal. No toxic effects were observed at the end of the two year study. Comparable results were found by Shubick, et al. (3) when various paraffin waxes were fed to rats at a dose of 10 percent of their diet.

The effects of applying petrolatum to the skin was tested on mice by applying approximately 60 microliters of the compound to the interscapular area (4). The different subfractions of petrolatum were also tested. The treatments consisted of by-weekly application of the material for the life of the animal. The results for petrolatum showed no significant tumorigenic effects when compared to the control group. However, the aromatic fraction of the petrolatum was observed to be carcinogenic at a concentration 50 times that at which it was present in the starting material. It should be noted that the petrolatum used in this study was amber or yellow petrolatum which contained a larger amount of the hydrocarbon fraction than those blends used in the Oser (2) study.

The subcutaneous effects of different petrolatum blends were tested on mice by injecting a single dose of 100 mg of the compound into the interscapular region (2). At the end of 9 months, the mice were sacrificed and observed for histological changes. No significant changes were

noted. In a similar study by Shubick, et al. (3) various blends of petroleum wax in the form of disks were implanted subcutaneously in mice. The results were comparable, i.e. for a similar period of implantation no histological changes were observed.

VI. Environmental Toxicology:

There is no available data concerning the effects of petrolatum on the environment. It is not water soluble so aquatic transport is of little consequence (1). No important use exists industrially for this compound, thus occupational exposure is minimized. No specific hygienic standards exist for petrolatum. However, a closely related compound, paraffin wax, has a threshold limit value of 2 mg/m^3 which can be used as a hygienic guideline for petrolatum vapors.

VII. Recommendations:

With the information available, petrolatum appears to be toxicologically safe for use in solar energy heating and cooling units. Although this compound may be injurious to the respiratory system, these effects would only be observed at extremely high temperatures or if an aerosol of the compound was produced. The acute toxicity and environmental effects of petrolatum are virtually unknown and if industrial production is to increase, adequate data will be needed in order to determine hygienic standards.

Based on the information available, petrolatum is recommended for use in solar energy heating and cooling units.

References

1. National Academy of Sciences. 1972. Food Chemicals Codex. 2nd edition. Washington, DC.
2. Oser, Bernard, Mona Oser and Slever Carson. 1965. Toxicologic Studies of Petrolatum in Mice and Rats. Tox. and App. Pharm. 7:382-401.
3. Shubik, P., et al. 1962. Studies on the Toxicity of Petroleum Waxes. Tox. and App. Pharm. 4 (supplement): 1-62.
4. Lijinsky, William, Umberto Saffiotti and Philippe Shubik. 1966. Skin Tumorigenesis by an Extract of Amber Petrolatum. Tox. and App. Pharm. 8:113-117.
5. American Conference of Governmental Industrial Hygienists. 1974. Documentation of Threshold Limit Values. Third edition. Cincinnati, OH.
6. Chemical Abstracts. #57356c Vol. 74. Mohay, J. et al. Detection of Carcinogenic Substances in Hydrocarbons. Acta. Pharm. (Hungary).
7. Sax, Irving N. 1975. Dangerous Properties of Industrial Materials. Van-Nostrand-Rheinholdt Co.

TOXICOLOGICAL EVALUATION OF ALLYL CAPROATE

September 3, 1976

ABSTRACT

Allyl caproate has been in public use since 1920 in foods and as a fragrance in soaps and cosmetics without reported adverse effects. Animal studies have shown this chemical to be of a moderate toxicity when administered orally while dermal administration produces a slight irritative effect. Respiratory exposure is unlikely due to allyl caproate's high boiling point.

Based on the data available and its use in foods and fragrances, allyl caproate is recommended for use in solar energy heating and cooling units, however, it is recommended that preference be given to those chemicals more thoroughly researched and determined to be toxicologically safe.

I. Chemical Properties:

Name: allyl caproate

Molecular formula: $\text{CH}_3 (\text{CH}_2)_4 \text{COOCH}_2 \text{CH} = \text{CH}_2$

Molecular weight (1): 156.25

Synonyms (1): allyl hexanoate; 2-propenyl n-hexanoate; hexanoic acid, allyl ester

Boiling point: 367°F

Refractive index (2): between 1.422 and 1.426 @ 20°C

Solubility (2): alcohol, fixed oils, mineral oil - miscible;
propylene glycol - practically insoluble

Specific gravity: 0.888

Odor: pineapple

Appearance (2): colorless to light yellow liquid

II. Hygienic Standards:

There are presently no available hygienic standards for allyl caproate.

III. Background:

Allyl caproate is one of a group of monocarboxylic unsaturated aliphatic esters (3). In general, esters are formed by removal of a hydrogen from an acid which is replaced by an organic grouping in a process known as esterification. Specifically, allyl caproate is formed by the esterification of caproic acid with allyl alcohol (4). This chemical has been in public use since the early 1920's as a flavoring agent and to impart a fragrance to soaps, detergents, etc. (2.4). In the United States, as of 1974, less than 5,000 pounds per year of allyl caproate were used in fragrances. As a flavoring agent, allyl caproate is accepted by the FDA

(21 CFR 121.1164) and was granted GRAS (generally recognized as safe) status by the Flavoring Extract Manufacturer's Association (1965) (4). This chemical does not appear to be of great industrial importance and no adverse health effects due to occupational exposures have been reported.

IV. Acute Toxicity:

Jenner, et al. (5), reported on the oral toxicity of allyl caproate using rats and guinea pigs. All doses were administered by intubation. An LD₅₀ for rats was observed to be 218 mg/kg with the time of death ranging from 4 hours to 18 hours. Toxic signs included depression and a scrawny appearance. Guinea pigs were reported to have an LD₅₀ of 280 mg/kg with the time of death ranging from 5 hours to 3 days. Depression and salivation was observed in the animals. Both of these LD₅₀'s indicate a moderate oral toxicity for allyl caproate.

In an unpublished report by Shelanski, as reported by Opdyke (4), the acute dermal LD₅₀ for allyl caproate indicates a high dermal toxicity, however, when applied full strength to the intact or abraded skin of a rabbit no irritation effects were observed.

V. Chronic Toxicity:

In an 18 week feeding study conducted by Hagan, et al., 100 mg/kg was fed by stomach tube to rats. The effects noted upon the liver were changes of a macroscopic and microscopic nature. The same study reported the effects of 1,000 ppm for 28 weeks and 2,500 ppm for 1 year of allyl caproate included in the diet of rats with no effects observed. Bär and Greipentrog, as reported by Opdyke (4), fed rats 0.1 percent to 0.5 percent allyl caproate in the diet for 2 years resulting in a suppression of

growth. The metabolism of allyl compounds in the rat is reported to be of a reaction between the compound and glutathione in the liver resulting in a metabolite which is readily excreted (4).

There have been no acute or chronic studies on the respiratory effects of allyl caproate but this mode of exposure is unlikely due to its high boiling point.

VI. Human Toxicity:

Human contact with allyl caproate includes its use as a fragrance in soaps and cosmetics and as a flavoring agent in foods. The irritating and sensitizing effect of this chemical was tested on 25 human subjects in an unpublished report by Klingman, as reported by Opdyke (4). Allyl caproate was applied in a closed patch test using a 4 percent concentration of the chemical in petrolatum. After 48 hours, a mild irritation effect was observed.

V. Environmental Toxicology:

As best can be determined, there is no available literature on the effects of allyl caproate on the environment. Although it has been tested for use as a fungicide, its low production and minimal usage suggest that this chemical is presently not of environmental concern (7).

VI. Recommendations:

In view of the limited toxicity data available and its use in food and fragrances, allyl caproate appears to be toxicologically safe for use in solar energy units. It is suggested, however, that those chemicals more extensively researched and determined to be toxicologically safe have first priority for use in solar energy heating and cooling units.

References

1. National Institute for Occupational Safety and Health. 1975. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
2. National Academy of Sciences. Food Chemicals Codex. 2nd edition. Washington, D.C.
3. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers. John Wiley and Sons, Inc. New York.
4. Opdyke, D.L.S. 1973. Monographs on Fragrance Raw Materials. Fd. Cosmet. Toxicol. 12: 489-1081.
5. Jenner, P.M., et al. 1964. Food Flavorings and Compounds of Related Structure. I. Acute Oral Toxicity. Fd. Cosmet. Toxicol. 2: 347-373.
6. Hagan, E.C., et al. 1967. Food Flavorings and Compounds of Related Structures. II. Subacute and Chronic Toxicity. Fd. Cosmet. Toxicol. 5: 141-157.
7. Chemical Abstracts. #27539d Vol. 55. Maruzzella, C. Effects of vapors of aromatic chemicals on fungi. J. Pharm. Sci. 50: 665.

TOXICOLOGICAL EVALUATION OF ETHYL CINNAMATE

August 27, 1976

ABSTRACT

Ethyl cinnamate is an ester of cinnamic acid. Very little toxicological information exists but its use as a flavoring agent indicates a low toxicity. In general, other cinnamic acid derivatives were found to be practically non-toxic or only slightly toxic. There are no hygienic standards for this chemical and it does not appear to be of environmental concern at this time.

Based on the apparent low toxicity of this chemical, ethyl cinnamate is recommended for use in solar energy heating and cooling units. However, preference should be given to those chemicals more completely researched and demonstrated to be toxicologically safe.

I. Chemical Properties:

Name: ethyl cinnamate

Molecular formula: $C_6H_5CH:CHCOOC_2H_5$; $C_{11}H_{12}O_2$

Molecular weight: 176.22

Synonyms (1,2): ethyl phenylacrylate; cinnamyl ether; cinnamic acid, ethyl ester (trans); ethyl 3-phenylpropenoate

Boiling point: $520^{\circ}F$

Melting point (1): $12^{\circ}C$

Specific gravity: 1.045

Refractive index (1): $N_D = 1.5598$ @ $20^{\circ}C$

Solubility (1): water - insoluble; alcohol - soluble; ether - very soluble; acetone - very soluble; benzene - soluble; ordinary organic solvents - very soluble

Odor (2): faint and cinnamon-like; strawberry-like

Appearance (2): colorless, oily liquid

II. Hygienic Standards:

At present, there are no hygienic standards for ethyl cinnamate.

III. Toxicity:

Ethyl cinnamate is one of the many derivatives of cinnamic acid. The chemical diversity of these derivatives makes it difficult to generalize upon their toxicology. Ethyl cinnamate is used as a flavoring agent and has been found to be a constituent of several naturally occurring substances, one of which is cocoa (2,3).

There are very few studies available on the toxicity of ethyl cinnamate. In a Russian abstract, ethyl cinnamate is mentioned as being one of several synthetic flavoring substances tested for their toxicity (4). In general, the LD₅₀'s for the various phenylethanol and cinnamic alcohol derivatives ranged from 2.5 g/kg to 6.2 g/kg which indicates that these chemicals are practically non-toxic or only slightly toxic (4,5). There appears to be no accumulation of these chemicals in the body, however, cinnamates were found to decrease the activity of a cellular enzyme, fructose diphosphate aldolase, important in the glycolytic pathway. Another study reported the effects of carbonyl compounds on rat liver glutathione levels (6). Glutathione (GSH) is important in protein synthesis and other metabolic pathways. Ethyl cinnamate was administered intraperitoneally to female rats in a dose of 0.8 ml/kg which was 25 percent or less of the oral LD₅₀. This chemical was found to be one of those carbonyl compounds showing the least enzymatic reactivity with GSH (6). Although there is no available data on the inhalation of ethyl cinnamate vapors, this exposure is unlikely due to its high boiling point.

There is no information available on the environmental consequences of ethyl cinnamate. It is insoluble in water and, therefore, not a likely aquatic pollutant (1). It has been tested as a herbicide and found to be effective against such species as Artemisia vulgaris and Vicia sitiva which are of the sagebrush and legume family respectively (7). There appears to be no industrially important uses for this chemical and there have been no reports of any injurious effects of an occupational nature.

IV. Recommendations:

There is little documented evidence of the toxicological effects of ethyl cinnamate. From its uses and the available literature, ethyl cinnamate appears

to be fairly innocuous. Based on the limited toxicological information available, ethyl cinnamate is recommended for use in solar energy heating and cooling units, however, preference should be given to those chemicals which have been proven safe through more extensive research.

References

1. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Company, Cleveland, Ohio.
2. National Academy of Sciences. 1972. Food Chemicals Codex. 2nd edition. Washington, D.C.
3. Chemical Abstracts. #28595a. Vol. 79. Flament, B., et al. Research on aromas. XVI. Cocoa aroma. 3. Helv. Chim. Acta. (Switz).
4. Chemical Abstracts. #69039e. Vol. 82. Zaitsev, A.N.; N.L. Rakhmanina. Toxic properties of phenylethanol and cinnamic alcohol derivatives. Vopr. Pitan. (Russia).
5. National Academy of Sciences. 1959. Handbook of Toxicology. Vol. I. Acute Toxicology.
6. Boyland, E. and L.F. Chesseaud. The effect on rat liver glutathione levels. Biochem. Pharm. 19: 1526-1528.
7. Chemical Abstracts. #28246q. Vol. 79. Pagani, G., et al. Cinnamic acid derivatives with phytotoxic activity. I. Farmaco, Ed. Sci. (Italy).

TOXICOLOGICAL EVALUATION OF ACETYL TRIBUTYL CITRATE

June 8, 1976

ABSTRACT

Acetyl tributyl citrate is reported to be of low toxicity in studies involving acute oral doses in rats and cats and acute interperitoneal doses in mice. Chronic oral doses have shown no ill effects in rats and cats. At this time no hygienic standards exist for this chemical and there is no environmental data available. In view of the existing toxicological data, this chemical is considered safe for use in solar energy heating and cooling units. However, other well researched chemicals have been documented to be toxicologically safe and therefore, considering the limited information about acetyl tributyl citrate, these other chemicals are the preferred chemicals for use.

I. Chemical Properties:

Name: Acetyl Tributyl Citrate

Molecular formula: $\text{CH}_3\text{COOC}_3\text{H}_7 (\text{COOC}_4\text{H}_9)_3$ or
 $\text{C}_{25}\text{H}_{50}\text{O}_7 (\text{COOC}_4\text{H}_9)_3$

Molecular weight(1): 402

Synonyms(2): Tributyl Acetyl Citrate

Melting point(1): -80°C

Boiling point: 341°F

Freezing point: -75°F

Specific gravity: 1.046

Vapor pressure(1): 1 mm Hg @ 173°C

Viscosity at stated temperature (centipoises): 42.7 @ 77°F

Flash point: 400°F

Solubility(1): water - insoluble

Appearance(3): clear, colorless, oily fluid

Odor: none

II. Hygienic Standard:

Presently there are no available standards for exposure to acetyl tributyl citrate.

III. General Toxicology:

Acetyl tributyl citrate belongs to the family of citric esters (4). These esters are used as plasticizers. Due to citric esters having little or no toxicity, they are presently used in the food industry in plastic packaging (2). Acetyl tributyl citrate is the most widely used citrate for plasticizing polyvinyl chloride.

IV. Acute Toxicity:

Finkelstein, et al., administered oral doses of acetyl tributyl citrate, ranging from 10 - 30 ml/kg, to groups of rats (3). The largest dose corresponded to approximately 2 liters of the citric ester for an average human on a weight basis. No signs of systemic toxicity were observed. Doses of 30-50 ml/kg of acetyl tributyl citrate were administered similarly to cats. These doses corresponded to about 2-3.4 liters for an average man and again no systemic effects were observed. Myers, et al., injected mice interperitoneally with acetyl tributyl citrate and observed an LD₅₀ of more than 4000 mg/kg (5). Fassett (as reported by Patty) found an oral LD₅₀ of greater than 25 ml/kg for rats (1). The preceeding results are summarized in Table I.

Table I.

Acute toxicity data for acetyl tributyl citrate.

<u>Animal</u>	<u>Route of Exposure</u>	<u>LD₅₀ (ml/kg)</u>
rat	oral	>30
rat	oral	>25
cat	oral	>50
mouse	interperitoneal	>4000 mg/kg

The low toxicity of acetyl tributyl citrate at these large dose levels has been attributed to its insolubility in water which may interfere with its absorption (3). No information is available on the acute inhalation or dermal toxicity of this chemical. However, considering the low vapor pressure of the chemical respiratory exposure is highly unlikely.

V. Chronic Toxicity:

The chronic effects of acetyl tributyl citrate on growth was studied by feeding rats pellets mixed with 5 and 10% concentrations of the chemical for a period of 2 months. The results showed a decrease in the weight at the 10% concentration which was attributed to the frequent diarrhea that occurred with the higher concentrations (3). A blood count was made on the rats before and after the 2 month feeding with no observed differences. Histological sections were made of the heart, lungs, gastrointestinal tract, liver, pancreas, spleen and kidneys after the 2 months period. The treated rats showed no differences from the control rats. Cats were fed 5 ml/kg daily for the same 2 month period. No systemic effects were observed other than a decrease in body weight of 30% which was attributed to loose bowel movements. Chronic toxicity studies were done by Meyers, et al., where mice were injected interperitoneally with 900 mg/kg of acetyl tributyl citrate for 14 days (5). The effects observed were a decline in normal weight gain, a fall in RBC counts and hemoglobin levels. At the end of the 14 day period sections were made of the liver, kidney, and lung tissues and examined for pathological abnormalities of which none were observed. Acetyl tributyl citrate was found to have a local anesthetic action when tested on the conjunctival sac of a rabbit and found also to block neural transmission when drops of the chemical on cotton were applied to the sciatic nerve.

The results observed for acetyl tributyl citrate in chronic toxicity studies uphold the previous low toxicity findings since the only effects observed were at high dose levels. No information is available on chronic inhalation or dermal toxicity.

VI. Environmental Toxicology:

No information is available on the consequences of acetyl tributyl citrate in the environment other than its insolubility in water (1). Sax describes this chemical as an odorless powder and states that its hazard potential is slight due to acrid vapors which are emitted when the chemical is heated, thus providing a strong warning to those exposed (6). This chemical is used extensively in the plastic industry and to date no ill effects have yet been discovered or reported among workers exposed to the chemical (2).

VII. Recommendations:

With the information available, acetyl tributyl citrate appears to be toxic only at very large oral and interperitoneal doses. Inhalation is not a likely source of entry due to acetyl tributyl citrate's low vapor pressure. Environmentally, this chemical has not been researched and if production is to increase adequate data will be needed in order to determine hygienic standards. Based on the available literature, acetyl tributyl citrate can be considered to be toxicologically safe for use in solar energy heating and cooling units. It should be noted, however, that other chemicals have been extensively researched and determined to be safe from a toxicological viewpoint, therefore considering the paucity of information on acetyl tributyl citrate these other chemicals are preferred in the solar units.

References

1. Patty, Frank. 1963. Industrial Hygiene & Toxicology. Vol. II. Interscience Publishers, John Wiley & Sons, Inc. New York.
2. Lefaux, René. 1968. Practical Toxicology of Plastics. CRC Press, Chemical Rubber Co., Cleveland, Ohio.
3. Finkelstein, Murray; Harry Gold. 1959. Toxicology of the Citric Acid Esters: Tributyl Citrate, Acetyl Tributyl Citrate, Triethyl Citrate, and Acetyl Triethyl Citrate. Toxicology and Applied Pharm. 1: 283-298.
4. Casarett, Louis and John Doull. 1975. Toxicology. Macmillan Publishing Company.
5. Meyers, D.B.; J. Autian, W.L. Guess. 1964. Toxicity of Plastics Used in Medical Practice II: Toxicity of Citric Acid Esters Used as Plasticizers. 53: 774-877.
6. Sax, Irving N. 1975. Dangerous Properties of Industrial Materials. Van Nostrand-Rheinholdt Company.

TOXICOLOGICAL EVALUATION OF TRIBUTYL CITRATE

July 15, 1976

ABSTRACT

Tributyl citrate is reported to be of low toxicity in studies involving oral and interperitoneal acute doses in various small animals. Chronic oral and interperitoneal doses showed effects on weight gain only at high doses. At this time no hygienic standards exist for this chemical and there is very minimal environmental information available. In view of the existing toxicological data, this chemical is considered safe for use in solar energy heating and cooling units. However, other extensively researched chemicals have been documented to be toxicologically safe and therefore, considering the limited information available concerning tributyl citrate, these other chemicals are the preferred chemicals for use.

I. Chemical Properties:

Name: Tributyl Citrate

Molecular formula (1): $(\text{CH}_2\text{COOC}_4\text{H}_9)_2 \text{COHCOOC}_4\text{H}_9$; $\text{C}_{18}\text{H}_{32}\text{O}_7$

Molecular weight (2): 360.44

Synonyms (1,3): butyl citrate; 1,2,3-propane tricarboxylic acid;
2-hydroxy-; tributyl ester; citric acid; tributyl ester.

Freezing point: -4°F

Boiling point: 451°F

Melting point (2): -85°C

Specific gravity: 1.04

Flash point: 315°F

Auto-ignition point (1): 695°F

Vapor pressure (2): 1 mm Hg @ 170°C

Solubility (2): water - < 0.002 g/100 ml

Viscosity 25°C cps (4): 31.9

Appearance (4): clear, colorless, oily liquid

II. Hygienic Standards:

There are presently no available standards for exposure to tributyl citrate.

III. General Toxicology:

Tributyl citrate is one of the many esters of citric acid (5). These esters are incorporated as plasticizers in polyvinyl chloride materials used for packaging food because of their low toxicity (5,6). Recently tributyl citrate has also been used as a plasticizer in spray-on bandage products and tested as a detergent additive for use in removing oily stains from cotton-polyester textiles (7,8).

IV. Acute Toxicity:

The toxic and pharmacologic effects of tributyl citrate have been tested in a series of small animals. Meyers, et al. (9) first tested the general behavioral effects of a parenteral dose of 400 mg/kg of tributyl citrate on mice. A marked effect on the central nervous system was evidenced by an increase in the respiration rate and convulsions. The stimulatory effects of this chemical were noted by injecting rabbits intravenously with a 100 mg/kg dose which was observed to increase motor activity and respiration. Frogs were injected with 100 mg/kg in the ventral lymph sac resulting in a short period of clonic activity and elimination of all reflex activity. The LD_{50} doses for mice after administration interperitoneally was determined to be 2900 ± 210 mg/kg after 72 hours (9). When administered orally in doses ranging from 10 to 30 ml/kg to rats, no local gastrointestinal irritation or systemic effects were observed. These doses corresponded to approximately 2 liters of the citric ester on a weight basis for an average human. Doses were administered similarly to cats by stomach tube in amounts from 30-50 ml/kg. No systemic effects were observed, however, diarrhea did occur which subsided after 24 hours. These doses corresponded to about 2 to 3.4 liters for an average human on a weight basis. The preceeding results are summarized in Table I.

TABLE I.

Acute toxicity data for tributyl citrate.

<u>Animal</u>	<u>Route of Exposure</u>	<u>LD₅₀</u>
Mouse	Interperitoneal	2900 ± 210 mg/kg
Rat	Oral	> 30 ml/kg
Cat	Oral	> 50 ml/kg

Because of the results of the initial behavioral tests done by Meyers, et al. (9), the effect of tributyl ester on neural muscle transmission and CNS involvement was further tested. Rats were used to test neural muscle transmission by exposing the sciatic nerve and then applying drops of tributyl citrate on cotton to the nerve. Local nerve conduction was found to be blocked. To test CNS involvement, the sub-maximal contralateral reflex was found to have been blocked after tributyl citrate administration. The local anesthetic action of this chemical was tested by observing the corneal reflex of a rabbit. The conjunctival sac was filled with tributyl citrate thereby anesthetizing the corneal reflex. In another study to test the local anesthetic effect 0.1 ml of a 20 percent suspension of tributyl citrate was injected intradermally into the backs of guinea pigs which resulted in a 2 hour insensitivity reaction.

There is no available inhalation toxicity data on tributyl citrate. However, considering the low vapor pressure of the chemical, respiratory exposure is highly unlikely. The oral acute toxicity data available shows tributyl citrate to be of a low order of toxicity.

V. Chronic Toxicity:

The chronic studies available on tributyl citrate involve inter-peritoneal and oral administration of the chemical to mice, rats and cats. Meyers, et al. (9) injected mice interperitoneally with a dose of 580 mg/kg of tributyl citrate which equaled 1/5 of the LD₅₀ dose. The only effect noted was inhibition of normal weight gain. There was found to be no effect upon red blood cells, white blood cells, clotting times or hemoglobin levels. In those mice sacrificed and studied histopathologically, no adverse effects were reported. Finkelstein, et al. (4) fed rats at

levels of 5 and 10 percent of tributyl citrate mixed in with food pellets for a 6 week period. No effects were observed at the 5 percent level while some growth repression, presumably due to frequent diarrhea, was observed at the 10 percent level. There was found to be no effect on blood count or various histological sections made at the end of the feeding period. In the same experiment, cats were fed 5 ml/kg of tributyl citrate by stomach tube for 2 months. No changes were observed in appearance or behavior of the animals. The only difference noted between the treated and control animals was a decrease of approximately 30 percent in body weight once again thought to be a result of the diarrhea that developed with the high dose level. There were no observable changes noted in blood counts, blood chemistry or urine analysis.

VI. Environmental Toxicology:

There is presently no information available on the consequences of tributyl citrate in the environment. It is known that this chemical is practically insoluble in water, therefore aquatic transport is unlikely. Research involving the biodegradability of plastics has shown the test organism, Candida lipolytica, capable of attacking a wide range of plasticizers including tributyl citrate (10). The extent of environmental biodegradability, however, is still unknown. Sax (1) states that this chemical is a slight fire hazard when exposed to heat or flame but due to the high flash point this can be easily controlled. It is also mentioned that tributyl citrate can react with oxidizing materials and if a fire did occur, water, CO₂, dry chemicals or CCl₄ should be used to extinguish it.

VII. Recommendations:

Tributyl citrate appears to have a low order of toxicity both orally and interperitoneally with the only adverse results noted at high dose levels. The information available has shown this chemical to be anesthetic when injected subdermally. Although there is no present information available on inhalation toxicity, tributyl citrate's low vapor pressure makes this an unlikely source of entry. Environmentally, this chemical has not been researched completely and if industrial production is to increase, adequate data will be needed in order to determine hygienic standards. Based on the available literature, tributyl citrate can be considered to be toxicologically safe for use in solar energy heating and cooling units. It should be noted, however, that other chemicals have been extensively researched and determined to be safe from a toxicological viewpoint, therefore, considering the limited information on tributyl citrate, these other chemicals are preferred for use in solar heating and cooling units.

References

1. Sax, Irving N. 1975. Dangerous Properties of Industrial Materials. Von Nostrand - Reinholdt Company.
2. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers, John Wiley and Sons, Inc. New York.
3. Chemical Abstracts Vol. 80. Formula Index.
4. Finkelstein, Murray and Harry Gold. 1959. Toxicology of the Citric Acid Esters: Tributyl Citrate, Acetyl Tributyl Citrate, Triethyl Citrate and Acetyl Tributyl Citrate. Toxicology and Applied Pharm. 1: 283-298.
5. Lefaux, René. 1968. Practical Toxicology of Plastics. CRC Press, Chemical Rubber Co., Cleveland, Ohio.
6. Casarett, Louis and John Doull. 1975. Toxicology. Macmilan Publishing Company.
7. Luongo, M., et al. 1974. *In Vivo* Method for Determining Efficiency of Spray-On Bandages Containing Anti-Infectives. J. Pharm. Sci. 63: 1376-1379.
8. Chemical Abstracts. #122697e Vol. 80. Unilever, N.V. 1973. Powdered Detergent Compounds for Washing Clothes. Fr. Demande (German).
9. Meyers, D.B.; J. Autian and W.L. Guess. 1964. Toxicity of Plastics Used in Medical Practice II: Toxicity of Citric Acid Esters Used as Plasticizers. 53: 774-877.
10. Chemical Abstracts. #4681 Om Vol. 76. Osmon, J.L., et al. 1971. Candida lipolytica, a Non-Pathogenic Test Organism for Determining of Plastics. Develop. Ind. Micro.

TOXICOLOGICAL EVALUATION OF METHYL HEPTENONE

August 30, 1976

ABSTRACT

Methyl heptenone is one of a group of chemicals known as ketones. As is true of a number of these chemicals, methyl heptenone is a natural component of a variety of consumer products. In general, ketones are considered to be of a low toxicity except for the narcotic action of their vapors. The high boiling point of methyl heptenone makes this mode of exposure unlikely.

Based on the natural occurrence of this chemical, its use as a flavoring agent and the general toxicity of ketones, methyl heptenone is recommended for use in solar energy heating and cooling units. However, it is suggested that those chemicals more completely researched and determined to be toxicologically safe have first priority for use in solar energy units.

I. Chemical Properties:

Name: methyl heptenone

Molecular formula: $(\text{CH}_3)_2 \text{C} = \text{CH} (\text{CH}_2)_2 \text{COCH}_3$

Molecular weight (1): 126.20

Synonyms: 6-methyl - 5 - hepten - 2 - one

Boiling point: 343°F

Melting point (2): -67°C

Freezing point: -87°F

Specific gravity: 0.860

Refractive index (2): $N_D = 1.4445$

Solubility (1,2): water - insoluble; alcohol, chloroform, ether - miscible

Appearance (1): yellow liquid

Odor (1): sharp citrus - lemongrass odor

II. Hygienic Standards:

There are presently no available hygienic standards for methyl heptenone.

III. Toxicity:

Methyl heptenone is one of a diverse group of chemicals known as the ketones. In general, the ketones are prepared from the oxidation of secondary alcohols by means of high temperatures and various catalyses (3). These chemicals are components of a variety of natural products and are encountered in the manufacture of varnishes, plastics, rubber, lubricating oils, cosmetics, pharmaceuticals, perfumes and organic compounds (4). Industrially, ketones are used primarily as solvents. Methyl heptenone is

not widely used industrially but finds use primarily as a flavoring agent and in fragrances (1,5). It is found most frequently as a naturally occurring component rather than a food or fragrance additive. The available literature involves the chemical detection of methyl heptenone in such things as wines, beer, various citrus oils, insects, flower oils, coffee, and tobacco, to name just a few (5).

There is no available literature on the toxicology of methyl heptenone. The natural occurrence of this chemical in products frequently consumed and used by the public would indicate a low order of toxicity. In general, there are no reports of acute injury for any of the industrially used ketones, which can be explained by their odorous warning properties (4). The toxicity, irritation and narcotic potency of the aliphatic ketones tend to increase with molecular weight and unsaturation. The dermal effect, in general, is a defatting action upon the skin causing it to chap and, therefore, become more susceptible to invasion by other materials. Although the narcotic action of the ketones is the most important consideration of their toxicology, the high boiling point of methyl heptenone makes this route of exposure unlikely (2). Excretion of the ketones, in general, is primarily through the lungs and kidneys (4). Ketones normally occur in small amounts in the blood and urine but little else is known of their metabolism.

IV. Environmental Toxicology:

There is no available literature on the consequences of methyl heptenone in the environment. It has been tested as a fungicide but not used to any great extent in the environment (6). The insolubility of this chemical in water indicates that aquatic transport would be unlikely (2). In general, the ketones are chemically stable but all are flammable to

a certain degree. Caution should therefore be taken when handling methyl heptenone near ignition sources (4).

VI. Recommendations:

It would appear that the primary toxicological concern when dealing with ketones is the narcotic effect of their vapors. Since methyl heptenone has such a high boiling point, the narcotic effect due to vapor exposure is extremely remote. Furthermore, the ubiquity of methyl heptenone in natural products of consumer use would indicate a low order of toxicity.

Based on its uses and the general toxicity of ketones, methyl heptenone is recommended for use in solar energy heating and cooling units. However, it is suggested that those compounds more completely researched and determined to be toxicologically safe have first priority for use in solar energy units.

References

1. National Academy of Sciences. 1972. Food Chemicals Codex. 2nd edition. Washington, D.C.
2. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Company. Cleveland, Ohio.
3. Hart, Harold and Robert Schuetz. Organic Chemistry: A Short Course. 4th edition. Houghton Mifflin Company. Boston, Massachusetts.
4. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers. John Wiley and Sons, Inc. New York.
5. Chemical Abstracts. Index. 1967-1971; 1972-1973; 1974-1975.
6. Chemical Abstracts. #27539d Vol. 55. Maruzzella, C. Effects of vapors of aromatic chemicals on fungi. J. Pharm. Sci. 50: 665.

TOXICOLOGICAL EVALUATION OF ISOBUTYL SALICYLATE

August 12, 1976

ABSTRACT

Isobutyl salicylate is one of a group of chemicals known as the salicylates. These chemicals are used primarily as analgesics and anti-pyretics. In general, the toxicity of the salicylates appears to be moderate, however, there is no available data on the specific toxicity of isobutyl salicylate.

Isobutyl salicylate is recommended for use as a heat exchange medium for solar energy heating and cooling units. Considering that toxicological information on this chemical is extremely limited, other more thoroughly researched substances are recommended over isobutyl salicylate.

I. Chemical Properties:

Name: isobutyl salicylate

Molecular formula: $\text{HOC}_6\text{H}_4\text{COOCH}_2\text{CH}(\text{CH}_3)_2$; $\text{C}_{11}\text{H}_{14}\text{O}_3$

Molecular weight (1): 194.23

Synonyms (1): 2-hydroxybenzoic acid, isobutyl ester

Melting point (1): 5.9°C

Boiling point: 498°F

Specific gravity: 1.064

Refractive index (1): 1.5087 @ 20°C

Solubility (1): water - insoluble; alcohol - soluble; ether - soluble

Appearance (2): colorless liquid

Odor (2): orchid

II. Hygienic Standards:

There are at present no hygienic standards for isobutyl salicylate.

III. Background:

Isobutyl salicylate is one of a group of compounds known as the salicylates. These chemicals are noted for their usefulness as analgesics and antipyretics. Derivatives of salicylic acid, such as acetylsalicylic acid (aspirin), methyl salicylate and salicylamide, are all included in this broad classification as well as isobutyl salicylate (3).

Several abstracts from Japan have mentioned isobutyl salicylate as being a preservative in soybean sauce and fermented soy sauce and as a component of various antifungal preparations (4,5,6,7,8). The Food Chemicals Codex (2) lists this chemical as a flavoring agent.

IV. General Toxicity:

There is no available data on the toxicity of isobutyl salicylate. Dreisback (3) states that a fatal oral dose for any salicylate is approximately 0.4 g/kg to 0.5 g/kg. In general, salicylates in toxic doses stimulate the central nervous system causing hyperpnea, lowering plasma prothrombin and increasing the body's production of organic acids. Absorption of the salicylates occurs readily through the gastrointestinal tract with excretion occurring almost entirely through the kidneys.

V. Environmental Toxicity:

Little is known about the consequences of isobutyl salicylate upon the environment. It is insoluble in water and, therefore, not a likely aquatic pollutant. There appears to be little or no industrial use for this chemical.

VI. Recommendations:

Isobutyl salicylate is one of a group of salicylates used in general in the pharmaceutical industry. The toxicity of the group appears to be moderate, however, there is no available data on the specific toxicity of isobutyl salicylate. Considering this relative moderate toxicity, isobutyl salicylate is suitable for use in solar energy heating and cooling units. Since there is extremely limited toxicological information available on this chemical, other more thoroughly researched substances are recommended over isobutyl salicylate.

References

1. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Co., Cleveland, Ohio.
2. National Academy of Sciences. 1972. Food Chemicals Codex. 2nd Edition. Washington, D.C.
3. Dreisback, Robert. 1974. Handbook of Poisoning. 8th Edition. Lange Medical Publications. Canada.
4. Chemical Abstracts. #5716a Vol. 59. Ueno, R. Antifungal compositions containing p-hydroxybenzoic acid esters. (applied patent - Japan).
5. Chemical Abstracts. #7893e Vol. 65. Tokeda, R., et al. Utilization of new anti-mold preparations for soy sauce. Shokwhin Shikenjo Itokoku (Japan).
6. Chemical Abstracts. #8960e Vol. 63. Tanekawa, E. Complete Utilization of Squid. XXIV. The manufacture of smoked meat. Cleaning of a squid processing factory in order to prevent the growth of mold. Hokkaido Daigaku Suisan Gakubu Kenkyu Iho.
7. Chemical Abstracts. #122432d Vol. 69. Wang, T. et al. Simple and rapid paper chromatography determination of preservatives and mimosine in soybean sauce. Chung Kuo Nung Yeh Hua Hyneh Hui Chih.
8. Chemical Abstracts. #7563v Vol. 69. Amano, T. Preservatives for shoyu (fermented soy sauce) VII. Determination of preservatives by gas chromatography. Nippon Shokuhin Kogyo Gakkaishi.

TOXICOLOGICAL EVALUATION OF BUTYL OLEATE

September 3, 1976

ABSTRACT

Butyl oleate is a long chain unsaturated fatty acid ester formed by the esterification of oleic acid and butyl alcohol. This chemical is not of great industrial importance although it has had some use as a plasticizer and emulsifier. No animal studies have been done nor are there any reports of human injury from exposure to butyl oleate. In general, the aliphatic esters are relatively inert. There are no hygienic standards for this chemical and it does not appear to be of environmental concern at this time.

In view of the limited toxicological information available, butyl oleate is recommended for use in solar energy heating and cooling units, however, preference should be given to those chemicals more completely researched and determined to be toxicologically safe.

I. Chemical Properties:

Name: butyl oleate

Molecular formula: $\text{CH}_3 (\text{CH}_2)_7 \text{CH} = \text{CH} (\text{CH}_2)_7 \text{COOC}_4\text{H}_9$ or

Molecular weight (1): 338.58

Synonyms (1): 9-Octadecenoic acid (cis), butyl ester (cis)

Boiling point: 343°F

Freezing point: -16°F

Melting point (1): -26.4°C

Specific gravity: 0.873

Flash point: 356°F

Refractive index (1): $N_D = 1.4480$

Solubility (1): water - insoluble; alcohol - soluble

Appearance (1,2): yellow liquid

Odor: mild

II. Hygienic Standards:

There are presently no available hygienic standards for butyl oleate.

III. Toxicology:

Butyl oleate is one of the many compounds known as esters (3). In general, an ester is formed by the removal of a hydrogen from an acid which is then replaced by an organic grouping in a process known as esterification. More specifically, butyl oleate is formed by the esterification of oleic acid and butyl alcohol. Unlike other long chain unsaturated fatty acid esters, which are used as solvents, lubricants and plasticizers, butyl oleate finds limited use as a plasticizer for vinyl chloride and as an

emulsifier for makeup (3,4,5,6).

In general, the aliphatic esters used as plasticizers are practically all inert (3). Some may cause irritation when inhaled as a vapor or when prolonged skin exposure occurs. Although little actual data is available, the hydrolysis of esters to normal metabolites or to other substances readily excreted in the urine indicates a low order of toxicity. In the case of butyl oleate, hydrolysis would result in the formation of oleic acid which is a known component of many fatty foods, and butyl alcohol which is a highly toxic substance.

For all practical purposes, the specific acute or chronic toxicity of butyl oleate is unknown. There are no available animal studies and the only reference to its use by humans involves its use as an emulsifier in a makeup which was reported to show no irritative effects to the skin (6). Although there are no inhalation studies available, this route of exposure is unlikely because of butyl oleate's high boiling point.

There is presently no available information on the consequences of butyl oleate in the environment. It is known that this chemical is insoluble in water, therefore, aquatic transport is unlikely. Research involving the biodegradability of plastics has shown that the test organism, Candida lipolytica, is capable of attacking a wide range of plasticizers including butyl oleate (7). The extent of environmental biodegradability, however, is still unknown. Sax (2) states that this chemical is a slight fire hazard when exposed to heat or flame but due to the high flash point this can be easily controlled. It is also mentioned that butyl oleate can react with oxidizing materials and if a fire occurs, water, CO₂, dry chemicals or CCl₄ should be used to extinguish it.

IV. Recommendations:

The general toxicity of the family of compounds that butyl oleate belongs to appears to be of a fairly low order. The actual toxicity of this chemical is not known, thus care should be taken when using it. The limited use of this chemical indicates that it is not industrially important or of environmental concern. Based on the limited information available, butyl oleate is recommended for use in solar heating and cooling units, however, preference should be given to those chemicals which have been proven safe through more extensive research.

References

1. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Company. Cleveland, Ohio.
2. Sax, Irving. 1975. Dangerous Properties of Industrial Materials. Van Nostrand - Reinholdt Company.
3. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers, John Wiley and Sons, Inc. New York.
4. Chemical Abstracts. #12183a. Vol. 60. Riser, G.R., et al. Evaluation of butyl stearate, butyl oleate, butyl ricinoleate, and methyl linoleate as poly (vinyl chloride) plasticizers. J. Am. Oil Chemists Soc.
5. Chemical Abstracts. #P15752x. Vol. 80. Ito, I. Antistatic poly (vinyl chloride). Ger. Offen. 2,310,277.
6. Chemical Abstracts. #P151577e. Vol. 78. Boublik, V. Emulsion makeup. Czech. 145,883.
7. Chemical Abstracts. #46810m. Vol. 76. Osmon, J.L., et al. 1971. Candida lipolytica, a non-pathogenic test organism for determining of plastics. Develop. Ind. Micro.

TOXICOLOGICAL EVALUATION OF METHYL PHENYLACETATE

August 4, 1976

ABSTRACT

Methyl Phenylacetate is one of many acetic acid esters known as acetates. It is used as a flavoring agent and fragrance material but has not received extensive commercial use in its 50 year history. Very limited toxicological data has been generated for methyl phenylacetate. That which does exist indicates that the chemical has a very low order of toxicity from the oral and dermal routes of exposure. Although the chronic and environmental toxicologies of methyl phenylacetate are not known, it is generally regarded as safe.

In view of the toxicological information currently available, Methyl Phenylacetate is recommended for use as a heat exchange medium for solar heating and cooling. However, this recommendation is made on limited toxicological data and preference should be given to chemicals that have had their toxic potentials more thoroughly investigated.

I. Chemical Properties:

Name: Methyl Phenylacetate

Molecular Formula: $C_6H_5CH_2COOCH_3$

Molecular Weight: 150.18 (2)

Synonyms: Acetic acid, phenylmethyl ester, Phenylacetic acid, methyl ester, Methyl alpha-toluate (3)

Boiling Point: 424°F, 218°C (2)

Specific Gravity: 1.062

Refractive Index: $N_D = 1.5075$ @ 20°C (2)

Solubility: Insoluble in water, soluble in all proportions in alcohol, ether, and acetone (2)

Physical State: Colorless liquid with a strong honey-like odor (1)

II. Hygienic Standards:

There are presently no available standards for exposure to methyl phenylacetate.

III. Toxicology:

Methyl phenylacetate is one of many esters of acetic acid known as acetates. It is commercially manufactured by methanolic esterification of phenylacetic acid with methanol (4). In the United States, this compound has been in public use since before 1920 as a flavoring agent and a fragrance material. Its most popular usage currently is as a fragrance material, with average yearly U.S. consumption being about 5,000 pounds (4). This low figure indicates that methyl phenylacetate has not found widespread

commercial application in its 50 year history. When used as a fragrance material, it is most commonly found in soaps, detergents, creams, lotions, or perfumes at maximum concentrations of 0.8 percent (4).

The toxicology of methyl phenylacetate is extremely vague. Very limited toxicological data is currently available due to the sparse commercial use of the chemical. Some generalizations can be made about the acetates, however, the chemical family to which methyl phenylacetate belongs. At higher concentrations, the physiological effects of acetate exposure are similar in both humans and experimental animals. First signs of intoxication are irritation of the eyes, nose, and throat followed by a relatively slow and gradual onset of narcosis with slow recovery after exposure ceases (5). In addition, some of the acetates have the ability to hydrolyze *in vivo*, causing an acidosis. None of the fragrance acetates have given rise to any health problems in manufacturing, handling, or in their end uses. Skin sensitization appears to be rare (5).

From the limited data available, the toxicology of methyl phenylacetate appears to resemble that of the rest of the fragrance acetates. Unpublished reports submitted to the Research Institute for Fragrance Materials and cited by Opdyke (4) supply the only toxicological data available for methyl phenylacetate. Conducted in 1974, all of the tests concern the acute toxicity of the chemical. LD₅₀ values are listed for oral and dermal exposures in experimental animals. The oral LD₅₀ in rats was given as 2.55 g/kg, while the dermal LD₅₀ for rabbits was reported as 2.4 g/kg. In addition, skin sensitization and irritation tests were conducted on humans as well as experimental animals. Methyl phenylacetate applied full strength to intact rabbit skin was only slightly irritating in a 24-hour period. In humans, 8 percent of solutions of methyl phenylacetate in petrolatum produced no sensitization reactions or irritation

after a 48-hour closed-patch test. The data from these unpublished reports would seem to indicate that methyl phenylacetate is a fairly innocuous compound with an acute toxicity of a relatively low order.

The chronic toxicity of methyl phenylacetate is not known. In 1968, the Joint FAO/WHO Expert Committee on Food Additives attempted to establish an Average Daily Intake (ADI) for methyl phenylacetate. The ADI is the amount of chemical additive that can be consumed daily in food without adverse effect on human health. The Committee was unable to arrive at an ADI for methyl phenylacetate because of a complete lack of chronic toxicological data (6). However, methyl phenylacetate was granted Generally Regarded As Safe (GRAS) status by the Flavor Extract Manufacturers Association in 1965 and has been approved by the Food and Drug Administration (FDA) for food use (21 CFR 121.1164) (4).

The environmental toxicology of methyl phenylacetate is also unknown. Neither its biodegradability nor its ability to biomagnify in the food chain have been researched. However, the chemical has not been reported to occur in nature so any detectable environmental concentrations would be due solely to man's activities (4). The toxicology of methyl phenylacetate in the industrial environment is also unspecified, although Patty (5), as previously stated, has found none of the fragrance acetates to cause any health problems in their manufacture or handling.

IV. Recommendations:

On the basis of toxicological information currently available, Methyl Phenylacetate is recommended as a heat exchange medium for solar heating and cooling. Although limited data exists on the toxic potential of this chemical, all of it suggests that methyl phenylacetate can be considered rather innocuous, at least from the standpoint of acute exposure.

Even though the chronic and environmental toxicities of methyl phenylacetate are not documented, the compound is generally regarded as safe.

In conclusion, it should be noted that recommendation of this chemical as a heat exchange medium is made on very limited toxicological data. Other chemicals that have received more thorough toxicological evaluations should be shown preference over methyl phenylacetate which has not received in depth study of its toxic potentials.

References

1. National Academy of Science. Food Chemicals Codex: Second Edition. National Research Council Publication 1406. Washington, D.C. 1972.
2. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
3. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
4. Opdyke, D.L.J. Monographs on Fragrance Raw Materials: Methyl Phenylacetate. Food and Cosmetics Toxicology. Volume 12 Supplement. pp. 941-942. 1974.
5. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
6. Joint FAO/WHO Expert Committee on Food Additives. Specifications for the Identity and Purity of Food Additives and Their Toxicological Evaluation: Some Flavoring Substances and Non-nutritive Sweetening Agents. World Health Organization Technical Report Series. No. 383. 1968.

TOXICOLOGICAL EVALUATION OF BENZYL FORMATE

July 23, 1976

ABSTRACT

Benzyl Formate is one of the saturated aliphatic esters of formic acid. Although the chemical is not of great industrial importance, it has had some use as a solvent and as a synthetic flavoring agent. The specific toxicology of benzyl formate is unknown. No animal studies of consequence have been done, nor have there been any reports of human injury from exposure to the chemical. Some generalizations about the toxicology of benzyl formate can be made from information available on the aliphatic saturated ester family. They are considered to display a fairly low order of toxicity for all types of exposure. The usual physiological effects of exposure to these esters are anesthesia and irritation of the eyes and respiratory membranes at high dose exposure levels. The formates are especially known for their irritant capabilities at high concentrations.

In view of toxicological information currently available, benzyl formate is recommended for use as a heat exchange medium for solar heating and cooling. However, preference should be given to chemicals which have been proven toxicologically safe from more complete research.

I. Chemical Properties:

Name: Benzyl Formate

Molecular Formula: $C_6H_5CH_2COOH$

Molecular Weight: 136.16 (2)

Synonyms: Formic Acid, Benzyl Ester, Benzyl Alcohol, Formate

Benzyl Methanoate (3)

Boiling Point: $397^{\circ}F$, $202^{\circ}C$ (2)Melting Point: $3.6^{\circ}C$ (1)

Specific Gravity: 1.085

Refractive Index: $N_D = 1.5154$ @ $20^{\circ}C$ (2)Vapor Pressure: 10 mm Hg @ $84^{\circ}C$ (4)Vapor Density (Air = 1): 4.7° (4)

Solubility: Very slightly soluble in water, soluble in alcohol, ether, and acetone, miscible with castor and linseed oils, and aromatic and petroleum hydrocarbons (1,2).

Physical State: Colorless liquid with a fruity, spicy odor (1)

At $25^{\circ}C$ and 760 mm Hg: 1 ppm = 5.56 mg/m^3

1 mg/liter = 180 ppm (4)

II. Hygienic Standards

There are presently no available standards for exposure to benzyl formate.

III. Toxicology:

Benzyl Formate is one of many members of the chemical family known as esters. Esters are formed when the hydrogen of an acid is replaced by an organic grouping in a process known as esterification (4). The reaction is often reversible, the reverse reaction referred to as hydrolysis. More specifically, benzyl formate is a saturated aliphatic ester of formic acid. Unlike other formic acid esters which have industrial importance as solvents, benzyl formate finds only sparse usage in the lacquer and food industries. Its application in the lacquer industry is as a solvent, while in the food industry it is used as a synthetic flavoring agent (1,5).

In general, the saturated aliphatic esters display a similar toxicology. Their most noted physiological effect is anesthesia when inhaled in sufficiently high concentrations. The degree of anesthetic action that the esters produce depends upon their water solubility. In addition, most of the aliphatic esters possess some degree of irritant action on exposed surfaces. The formates are especially irritating to the eyes and respiratory tract because of their ability to hydrolyze when in contact with moist surfaces, forming the original alcohol and formic acid. The effects of dermal contact with aliphatic esters is usually defatting and cracking, while sensitization dermatitis is rare if seen at all (4).

For all practical purposes, the specific toxicology of benzyl formate is unknown. Limited toxicological literature could be found on the chemical. The Registry of Toxic Effects of Chemical Substances (3) lists two acute toxicity values for benzyl formate. An oral LD₅₀ for rats is given as 1,700 mg/kg, and a dermal LD₅₀ value in rabbits is listed as 2,000 mg/kg. However, an attempt to obtain the literature from which this data was extracted was unsuccessful as referenced by the Registry.

If, in fact, the acute toxicity values appearing in the Registry are valid, the toxic potential of benzyl formate from acute exposure could be considered slight.

Nothing is known of the chronic toxicity of benzyl formate. No long-term studies of its toxic effects in animals have been made and there have been no reports of any injurious effects in humans (1). However, benzyl formate is not considered to be hazardous when consumed over long periods in foods. The FDA has approved benzyl formate as a synthetic flavoring agent (21 CFR 121.1164), and it is generally regarded as safe (GRAS) by the Flavor Extract Manufacturers Association (5).

The environmental toxicity of benzyl formate is unknown. To date, no studies have been carried out to assess its biodegradability or its potential to biomagnify in the food chain. It should be noted, however, that it would be unlikely to observe benzyl formate as an ester in the environment because of its ability to hydrolyze to alcohol and formic acid. The toxicology of benzyl formate in the industrial environment also has not been specified. In general, however, the saturated aliphatic esters are considered to be among the least toxic of industrial solvents in use, their only observed adverse effect being irritation of the eyes and respiratory tract (4).

IV. Recommendations:

On the basis of toxicological information currently available, benzyl formate is recommended for use as a heat exchange medium for solar heating and cooling. It would appear that both the acute and chronic toxicities of this chemical would be of a fairly low order. However, this recommendation is made almost entirely on the general toxicity of

saturated aliphatic esters, not on data on the specific toxicology of benzyl formate. Although it is reasonable to suspect that benzyl formate exhibits a toxicology similar to other aliphatic esters, the real toxic potential of benzyl formate is not known and caution should be taken when using the compound. For these reasons, even though benzyl formate should not create unreasonable hazards as a heat exchange medium, preference should be given to chemicals which have been proven safe through more extensive research.

References

1. Browning, E. Toxicity and Metabolism of Industrial Solvents. Elsevier Publishing Company. Amsterdam. 1965
2. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
3. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
4. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
5. Furia, T.E. Handbook of Food Additives. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1968.

TOXICOLOGICAL EVALUATION OF METHYL BENZOATE

September 7, 1976

ABSTRACT

Methyl benzoate was in public use before the 1900's in foods and as a fragrance in soaps and cosmetics without reported adverse effects. Animal studies have shown this chemical to be of a low order of toxicity at acute levels. The limited chronic toxicological data available suggests that at high dose levels the central nervous system may be adversely affected. An environmental study in Russia resulted in a proposal to limit concentrations in water storage reservoirs to 0.1 mg/l based on the taste and odor of methyl benzoate rather than its toxicity. Consideration should be given to the 181⁰F flash point of this chemical since it is below the expected operating temperatures of solar energy units and could possibly result in a fire hazard. Toxicologically, this chemical is safe for use in solar energy units. However, bearing in mind the potential of a fire hazard, it is recommended that those chemicals determined to be toxicologically safe and with flash points above the suggested operating temperatures have first priority for use in solar energy heating and cooling units.

I. Chemical Properties:

Name: methyl benzoate

Molecular formula: $C_6H_5COOCH_3$

Molecular weight (1): 136.16

Synonyms (3): niobe oil; methyl benzenecarboxylate; benzoic acid, methyl ester

Boiling point: 389°F

Melting point (1): -12.3°C

Freezing point: 10°F

Specific gravity: 1.085

Flash point: 181°F

Refractive index (1): $N_D = 1.5164$ @ 20°C

Solubility (1,4): water - insoluble; alcohol, ether, methyl alcohol - soluble; oil - miscible; glycerin - insoluble

Vapor pressure (2): 1 mm Hg @ 39°C

Vapor density (air = 1) (2): 4.7

Appearance (4): colorless liquid

Odor (4): fruity

II. Hygienic Standards:

There are presently no available standards for exposure to methyl benzoate.

III. General Toxicology:

Methyl benzoate is one of a group of aromatic monocarboxylic acid esters (5). These simple aliphatic esters of benzoic acid have uses as solvents, flavorings and in perfumes and fragrances. Although the metabolism of these esters is not yet understood, a low order of toxicity is indicated by the relatively high acute lethal dose levels. Respiratory exposure is unlikely due to the high vapor pressures of these chemicals. No adverse health effects have been reported among those who have been exposed industrially to these esters (2,5).

Methyl benzoate is prepared from the esterification of methyl alcohol and benzoic acid (6). It occurs naturally in various flower oils, e.g., tuberose, orchids, ylang-ylang and cloves (6).

Industrially, this chemical is used to some extent in the lacquer industry (2). Methyl benzoate was in public use before the 1900's as a flavoring agent and to impart a fragrance to soaps, detergents, and cosmetics (4,6). In the United States, as of 1974, approximately 15,000 lbs./year of methyl benzoate were used in fragrances. As a flavoring agent, methyl benzoate is accepted by the FDA (21 CFR 121.1164) and was granted GRAS (generally recognized as safe) status by the Flavoring Extract Manufacturer's Association (1965) (6).

IV. Acute Toxicity:

Methyl benzoate is generally considered to be of a low toxic nature when administered orally. The results of various acute oral toxicity studies are shown in Table I.

Table I.
Acute oral toxicity values for methyl benzoate.

<u>Animal</u>	<u>LD₅₀ (g/kg)</u>	<u>Reference</u>
Rat	2.17	7
Rat	3.43	6
Rat	3.5	8
Rat	1.35	9
Mice	3.33	9
Mice	3.0	8
Rabbit	2.17	7
Guinea pig	4.1	8

Kravets-Beker, et al., as reported by Opdyke (6) and Chemical Abstracts (8), observed that sublethal doses of methyl benzoate increased leucocyte, erythrocyte and reticulocyte counts and prothrombin production time. This same study found that at a dose of 500 mg/kg of methyl benzoate, cholinesterase and ascorbic acid activity were reduced.

Although respiratory exposure is unlikely due to methyl benzoate's low vapor pressure, inhalation studies on rats using a saturated vapor for a period of 8 hours resulted in no observed lethal effects (5).

Studies conducted to determine the irritating qualities of methyl benzoate demonstrated a moderate irritating effect when applied to the skin (5). Graham, et al. (7), applied approximately 20 ml of methyl benzoate to a clipped area (4" x 6" x 7") on the back of 2 cats which resulted in the death of both after 21 hours. When applied to the eye of a rat, methyl benzoate appeared to be only slightly irritating compared to application of the chemical to the skin which resulted in a moderate irritating effect (5).

Valette and Lavier, as reported by Opdyke (6), observed that methyl benzoate was slow to penetrate the skin of rats.

V. Chronic Toxicity:

Very little data is available on the chronic effects of methyl benzoate. Kravets-Bekker, as reported by Opdyke (6) and Chemical Abstracts (8), found that chronic low doses for a period of 6 months showed no adverse effects. However, chronic high doses resulted in damage to the central nervous system. The method of administration was assumed to be oral for mice, rats, and guinea pigs. However, the exact dose levels were not reported.

VI. Human Toxicity:

Human contact with methyl benzoate includes its use as a fragrance in soaps and cosmetics, and as a flavoring agent in foods. The irritating and sensitizing effects of the chemical were tested on 25 human subjects (6). Methyl benzoate was applied in a closed patch test using a 4 percent concentration of the chemical in petrolatum. After 48 hours, no irritation or sensitization effects were observed. From this limited data, it appears that the dermal route of exposure is of little or no consequence with respect to humans.

VII. Environmental Toxicology:

The only available literature concerning the effects of methyl benzoate in the environment is a Russian abstract dealing with the sanitary indicators of this chemical in relation to water storage reservoirs (10). The threshold value for odor and taste of methyl benzoate in water was given respectively as 0.001 mg/l, and 0.0005 mg/l. The amount

of methyl benzoate affecting the organoleptic characteristics of fish meat was found to be 0.01 mg/l. The abstract then listed a limit value for the sanitary condition of reservoir waters which was determined to be 0.01 mg/l. This value appears to be based on methyl benzoate's odor and taste rather than its toxicity. At present, there are no standards or threshold limit values of exposure for methyl benzoate in the United States.

Sax (11) states that methyl benzoate may react with oxidizing materials and may become a moderate fire hazard when exposed to heat or flame. In solar energy units the potential for a fire hazard may exist because temperatures are often reached above 181°F which is the flash point for methyl benzoate.

VIII. Recommendations:

Based on the available toxicological data and its uses in foods and fragrances, methyl benzoate appears to be toxicologically safe for use in solar energy units. However, the potential of a fire hazard above 181°F suggests that methyl benzoate may not be suitable for the use intended since temperatures in solar heating and cooling units are often above this temperature.

In view of the potential fire hazard of methyl benzoate, it is recommended that those chemicals determined to be toxicologically safe and with flash points above the operating temperature of 200°F for solar energy units have first priority for use in solar energy heating and cooling units.

References

1. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Company. Cleveland, Ohio.
2. Browning, Ethel. 1965. Toxicity and Metabolism of Industrial Solvents. Elsevier Publishing Company. New York.
3. National Institute for Occupational Safety and Health. 1975. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
4. National Academy of Sciences. 1972. Food Chemicals Codex, 2nd edition. Washington, D.C.
5. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers, John Wiley and Sons, Inc. New York.
6. Opdyke, D.L.S. 1974. Monographs on Fragrance Raw Materials. Fd. Cosmet. Toxicol. Vol. 12. p. 937.
7. Graham, Boyd and Marvin Ruizenga. 1945. Toxicity Studies on Benzyl Benzoate and Related Benzyl Compounds. J. of Pharm. and Exp. Therp. 84: 358.
8. Chemical Abstracts. #18045b. Vol. 75. Kravets-Bekker, A.A., et al. Toxicological characteristics of methyl benzoate and potassium benzoate. Faktory Vnesh. Sredy Ikh Znachenie Zdorovya Naseleniya (Russia).
9. Jenner, P.M., et al. 1964. Food flavorings and compounds of related structure. I. Acute oral toxicity. Fd. Cosmet. Toxicol. 2: 327.
10. Chemical Abstracts. #98513w. Vol. 68. Bekker, A.K. Experimental study of sanitary indicators of the effect of methyl benzoate and potassium benzoate on reservoirs. Vop. Kommunal. Gig. (Russia).
11. Sax, Irving N. 1975. Dangerous Properties of Industrial Materials. Van Nostrand - Reinholdt Company.

TOXICOLOGICAL EVALUATION OF ETHYL BENZOATE

June 21, 1976

ABSTRACT

Ethyl benzoate has been in public use since 1940 in foods and as a fragrance in soaps and cosmetics without reported adverse effects. Animal studies have shown this chemical to be of a low order of toxicity at acute levels. There is, however, no chronic or environmental toxicity data available. Consideration should be given to the 200°F flash point of this chemical since this is well within the operating temperatures of solar heating and cooling units and could possibly result in a fire hazard. Bearing in mind this potential hazard and the limited toxicological information, it is recommended that those chemicals more completely researched and determined to be toxicologically safe have first priority for use in solar energy heating and cooling units.

I. Chemical Properties:

Name: Ethyl Benzoate

Molecular formula: $C_6H_5CO_2C_2H_5$

Molecular weight(1); 150.17

Synonyms: benzoic ether; benzoic acid, ethyl ester; Essence of Niobe.

Freezing point: $-27^{\circ}F$ Boiling point: $415^{\circ}F$ Melting point(1): $-34.6^{\circ}C$

Specific gravity: 1.043

Flash point: $200^{\circ}F$

Vapor density (air = 1) (1): 5.2

Refractive index(3): $N_D = 1.500$ @ $20^{\circ}C$

Solubility(3,5): water - insoluble; alcohol - soluble; ether - soluble; acetone - soluble; benzene - soluble; chloroform - soluble; petroleum - soluble; castor and linseed oils - miscible

Appearance(4,5): colorless liquid

Odor(4,5): pleasant but powerful fruity odor

II. Hygienic Standards:

There are presently no available standards for exposure to ethyl benzoate.

III. General Toxicology:

Ethyl benzoate is one of a group of aromatic monocarboxylic acid esters (1). These simple aliphatic esters of benzoic acid have uses as solvents, flavorings and in perfumes and fragrances (1,6). Although the metabolism of these esters is not yet understood, a low order of toxicity is indicated by the relatively high acute oral LD₅₀ dose levels. Respiratory exposure is unlikely due to the high vapor pressures of these chemicals (1). No adverse health effects have been reported among those who are exposed industrially to these esters.

Ethyl benzoate is prepared from the esterification of ethyl alcohol and benzoic acid (6). Industrially, ethyl benzoate is used as a solvent for cellulose nitrate and acetate, ethyl cellulose, ester gum and mastic shellac (4). It is also used in the lacquer industry and as a plasticizer. Ethyl benzoate has been in public use since 1940 as a flavoring agent and to impart a fragrance to soaps, detergents, etc. (5,6). In the U.S., as of 1974, less than 5000 lb/year of ethyl benzoate were used in fragrances. As a flavoring agent, ethyl benzoate is accepted by the FDA (21 CFR 121.1164) and was granted GRAS (generally recognized as safe) status by the Flavoring Extract Manufacturer's Association (1960) (6). Substances with the GRAS designation can be used as food additives but have yet to be reviewed and pronounced as safe under the Food Additive Amendment of 1958 (9).

IV. Acute Toxicity:

Based on the high oral dose levels necessary to achieve mortality in test animals, ethyl benzoate can be considered to be of a low toxic nature. The results of various acute oral toxicity studies are shown in Table I.

TABLE I.

Acute oral toxicity values for ethyl benzoate.

<u>Animal</u>	<u>LD₅₀ (g/kg)</u>	<u>Reference</u>
Rat	6.48	4
Rat	2.10	8
Rabbit	2.63	8

Although respiratory exposure is unlikely due to ethyl benzoate's low vapor pressure, inhalation studies using a saturated vapor with rats for a period of 8 hours resulted in no observed lethal effects (4).

Studies conducted to determine the irritating qualities of ethyl benzoate demonstrated a moderate irritating effect when applied to the skin (4). Graham, et al. (8), applied approximately 20 ml of ethyl benzoate to a clipped area (4" x 6" x 7") on the back of 2 cats which resulted in the death of both after 20 hours (8). The effect of 0.5 ml of undiluted ethyl benzoate on the eyes resulted in a very small area of corneal necrosis (4).

V. Human Toxicity:

Human contact with ethyl benzoate includes its use as a fragrance in soaps and cosmetics and as a flavoring agent in foods. The irritating and sensitizing effects of this chemical were tested on 25 human subjects (6). Ethyl benzoate was applied in a closed patch test using an 8% concentration of the chemical in petrolatum. After 48 hours, no irritation or sensitization effects were observed.

VI. Environmental Toxicity:

As can best be determined, there is no available literature on the effects of ethyl benzoate on the environment. Its low production and minimal usage suggest that this chemical is presently not of environmental concern.

Sax (10) states that ethyl benzoate may react with oxidizing materials and may become a moderate fire hazard when exposed to heat or flame. In solar energy units the potential for a fire hazard may exist because temperatures are often reached above 200°F which is the flash point for ethyl benzoate.

VII. Recommendations:

In view of low toxicity data and its use in foods and fragrances, ethyl benzoate appears to be toxicologically safe for use in solar energy units. However, potential of a fire hazard above 200°F suggests that ethyl benzoate may not be suitable for the use intended since temperatures in solar heating and cooling are often above this level.

Considering the absence of data regarding chronic and environmental toxicology, it is suggested that those chemicals already well documented and determined to be toxicologically safe have first priority for use in solar energy heating and cooling units.

References

1. Patty, Frank. 1963. Industrial Hygiene & Toxicology. Vol. II. Interscience Publishers, John Wiley & Sons, Inc. New York.
2. National Institute for Occupational Safety and Health. 1975 Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
3. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Co., Cleveland, Ohio.
4. Browning, Ethel. 1965. Toxicity and Metabolism of Industrial Solvents. Elsevier Publishing Company. New York.
5. National Academy of Sciences. 1972. Food Chemicals Codex. 2nd edition. Washington, D.C.
6. Opdyke, D.L.S. 1974. Monographs on Fragrance Raw Materials . Fd. Cosmet. Toxicol. Vol. 12. p. 703.
7. National Academy of Sciences. 1959. Handbook of Toxicology Vol. I; Acute Toxicology.
8. Graham, Boyd and Marvin Kuizenga. 1945. Toxicity Studies on Benzyl Benzoate and Related Benzyl Compounds. J. of Pharm. & Exp. Therp. 84: 358.
9. Casarett, Louis and John Doull. 1975. Toxicology. Macmillan Publishing Company. New York.
10. Sax, Irving N. 1975. Dangerous Properties of Industrial Materials. Van Nostrand - Rheinholdt Company.

TOXICOLOGICAL EVALUATION OF ISOBUTYL ISOBUTYRATE

August 27, 1976

ABSTRACT

Isobutyl isobutyrate is an ester of isobutyric acid and has limited use in perfumes, flavorings and as a solvent. Animal studies have shown this chemical to be of a low order of toxicity at acute levels. There is, however, no chronic or environmental toxicity data available. Consideration should be given to the 150°F flash point of this chemical since operating temperatures of solar energy heating and cooling units are above this which could possibly result in a fire hazard. Bearing in mind this potential hazard and the limited toxicological information available, this chemical is recommended for use in solar energy heating and cooling units with much reservation. Toxicologically those chemicals more thoroughly researched and documented to be safe are recommended for such use before isobutyl isobutyrate.

I. Chemical Properties:

Name: isobutyl isobutyrate (ICIB)

Molecular formula: $(\text{CH}_3)_2 \text{CHOOCH}_2\text{CH}(\text{CH}_3)_2$

Molecular weight (1): 144.24

Synonyms (1): isobutyric acid, isobutyl ester; 2-methylpropyl
isobutyrate; propanoic acid, 2-methyl, isobutyl ester

Boiling point: 297°F

Freezing point: -112°F

Melting point (2): -81.0°C

Specific gravity: 0.857

Vapor pressure (2): 10 mm. Hg @ 38°C

Vapor density (air = 1) (2): 5.0

Density of saturated air (air = 1) (2): 1.05

Flash point (2): 120°F

Refractive index (3): 99 @ 20°C

Solubility (2,3): water - slightly soluble (0.5g per 100 ml H_2O);
alcohol, ether, acetone - soluble

Odor: fruity

Appearance (4): liquid

II. Hygienic Standards:

There are presently no available standards for isobutyl isobutyrate.

III. General Toxicity:

Isobutyl isobutyrate is classified chemically as an ester (2). Esters are formed by replacing the hydrogen of an acid with an organic grouping. Isobutyl isobutyrate is an esterification of isobutyric acid where the

hydrogen is replaced by the isobutyl radical. In general, the esters of isobutyric acid are used in perfumes, flavorings and as solvents. Specifically, isobutyl isobutyrate has little use as a solvent but is used widely in perfumes and flavorings. Little is known of the toxicology of the butyrates but there have been no reports of problems associated with the industrial handling of these compounds. The ready hydrolysis of these chemicals to substances normally found in the diet suggest that these chemicals do not accumulate in the body.

IV. Acute Toxicity:

Very little data is available on the toxicity of isobutyl isobutyrate. What is available concerns only the acute toxicity of this compound. An oral lethal dose of isobutyl isobutyrate is given as 12,800 mg/kg for rats and mice (2). None of the animals were killed when given 6,400 mg/kg of the chemical. This indicates a low order of toxicity for oral exposure (2,5). Interperitoneal injection of isobutyl isobutyrate was found to kill rats at 6,300 mg/kg and mice at 1,600 mg/kg which indicates a slight toxicity. In an irritation test, reported by Patty (2), absorption of isobutyl isobutyrate by the skin was indicated. After a 24 hour exposure to an unknown concentration of this chemical a slight irritation reaction was observed in the test animal. Although inhalation is an unlikely source of exposure, due to the chemical's high boiling point, a lethal concentration of the vapors for rats was found to be 5,000 ppm after a 6 hour exposure. Symptoms at this dose level included narcosis and prostration. A similar exposure to 600 ppm results in no deaths or symptoms. Isobutyl isobutyrate appears to be practically nontoxic when inhaled.

V. Chronic Toxicity:

There is no available data concerning the chronic toxicity of isobutyl isobutyrate. The hydrolysis of this compound into components easily metabolized or already present in a normal diet indicate that there would be no accumulation of the chemical in the body, therefore, minimizing the potential for injurious effects over a long period of time (2).

VI. Environmental Toxicology:

The environmental toxicity of isobutyl isobutyrate is unknown. To date, no studies have been undertaken to determine its biodegradability. However, the slight solubility of this chemical indicates that there is a potential for this chemical to become an aquatic pollutant (3).

There appears to be no industrial problems regarding the handling of isobutyl isobutyrate (2). It is not of major industrial importance and no hygienic standards have been determined for it. From a safety standpoint, this chemical has a relatively low flash point of 120°F. Since operating temperatures in solar energy units are in excess of 200°F, a potential fire hazard may exist if the resulting vapors are allowed to come into contact with a source of ignition. Sax (4) states that isobutyl isobutyrate may be a slight hazard when exposed to heat or flame and it can react with oxidizing materials.

VII. Recommendations:

In view of the low order of acute toxicity and its reported use in perfumes and flavors, isobutyl isobutyrate appears to be toxicologically safe for use in solar energy units. However, potential of a fire hazard above 120°F suggests that isobutyl isobutyrate may not be suitable for the

use intended since the operating temperatures in solar heating and cooling units are well above this temperature.

Considering the absence of chronic and environmental toxicological data and the potential of a fire hazard, it is suggested that those chemicals already well documented and determined to be toxicologically safe have first priority for use in solar energy heating and cooling units.

References

1. National Institute of Occupational Safety and Health. 1975. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
2. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II., Interscience Publishers, John Wiley and Sons, Inc. New York.
3. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Company. Cleveland, Ohio.
4. Sax, Irving N. 1975. Dangerous Properties of Industrial Materials. Van Nostrand - Reinholdt Company.
5. National Academy of Sciences. 1959. Handbook of Toxicology. Vol. I., Acute Toxicities.

TOXICOLOGICAL EVALUATION OF PERCHLOROETHYLENE

August 6, 1976

ABSTRACT

Perchloroethylene belongs to a family of chemicals known as the aliphatic chlorinated hydrocarbons used in a variety of industries. This chemical is used primarily in industry as a solvent and is the drug of choice in treating hookworms of man and animals. Toxicologically, perchloroethylene exhibits a low order of acute toxicity, however, chronic exposure has shown it to cause liver and kidney damage as well as other systemic changes at moderate dose levels. Human experience with this chemical has shown it to be toxic only at high acute dose levels but chronic exposure to concentrations even lower than those of the threshold limit value may be a health hazard. There is little information of the effects of perchloroethylene upon the environment. On the basis of toxicological information available, perchloroethylene is recommended for use in solar heating and cooling units if extreme caution is taken in using the chemical.

I. Chemical Properties:

Name: Perchloroethylene (Tetrachloroethylene)

Molecular formula: $C_2 Cl_4$

Molecular weight (1): 165.82

Synonyms (13): Ankilostin; carbon bichloride; carbon dichloride;

Czterochloroethylen (Polish); Didakene; ENT 1860; ethylene

tetrachloride; NEMA; "per"; perchloorethyleen, per (Dutch);

perchloraethylen, per (German); perchlorethylene, per (French);

perclene; perchloroetiline (Italian); Persec; Phillsov; Perawin;

Tetracap; tetrachlooretheen (Dutch); tetrachloraethen (German);

tetrachoethene; 1,1,2,2, - tetrachloroethylene; tetrachoroethene

(Italian); tetrachloroethanol; Tetralex.

Freezing point: $-8^{\circ}F$

Boiling point: $250^{\circ}F$

Specific gravity: 1.625

Flash point: none

Refractive index (2): $n = 1.5053$ @ $20^{\circ}C$

Solubility (2): water - insoluble; alcohol, ether, benzene - soluble

Odor: ether-like

Appearance (3,4): colorless liquid

Vapor pressure (3): 19 mm Hg @ $25^{\circ}C$

Vapor density (air = 1) (3): 5.7

Percent in "saturated" air (4): 2.5 @ $25^{\circ}C$

Density in "saturated" air (4): 1.11 (air = 1)

II. Hygienic Standard:

TLV: Skin - 100 ppm = 670 mg/m³ (OSHA standard 1910.93).

The skin designation refers to the possible addition to over all exposure by absorption through the skin or mucous membranes in addition to that inhaled as a vapor.

III. General Toxicology:

Perchloroethylene belongs to a group of chemicals known as aliphatic chlorinated hydrocarbons which are used in a variety of industries (5). Chlorinated hydrocarbons are the principal means by which chlorine reaches the chemical market but they are probably best known for their solvent properties for oils, waxes, fats and other organic compounds. These solvent properties are incorporated in such uses as extractants, dry cleaning agents, surface degreasers, vehicles for paints, varnishes and other coatings. The chlorinated hydrocarbons are similar physiologically in that they first excite the central nervous system which may then lead to narcosis (6). Intoxication occurs generally by the inhalation of vapors (5).

Perchloroethylene is principally used as a solvent for oils, fats, resins and cellulose acetate (3). It is produced by treating pentachloroethane with mild alkalis. This chemical is used in the plastic, elastomer, printing and the textile industries as well as being a dry cleaning and degreasing agent. It is also the drug of choice in treating hookworms of man and animals and has been used agriculturally as a fungicide and insecticide (4,7,8). As with the other halogenated hydrocarbons, perchloroethylene is considered a narcotic and was once thought to be the least toxic of the chlorinated hydrocarbons, however, recent human and animal studies have shown this chemical to cause liver and kidney damage after chronic exposure (8,3,6). Industrial accidents with perchloroethylene have resulted in

death after both acute and chronic intoxication (3). This chemical is closely related to the controversial trichlorethylene that has recently been reviewed by the FDA due to reports of its potential carcinogenicity. While, to date, perchloroethylene is not suspected of being a carcinogen, its chemical similarity to trichloroethylene may indicate a similar biological response.

IV. Acute Toxicity:

Various animals have been used to study the acute effects of perchloroethylene with results varying greatly according to the method of administration. Early studies centered on the chemical's effect upon the liver when given orally. Schlingman, et al. (9) gave perchloroethylene in gelatin globules to various animal species in the amount of what he determined to be a therapeutic dose for the treatment of hookworm. It was determined that those animals with the more rapid elimination of the drug through the intestinal tract showed the least effects from the chemical. Cattle and horses were more susceptible to perchloroethylene and showed a slight amount of liver damage whereas sheep, foxes, cats, puppies and chickens, in the order of most to least susceptible, showed signs of liver damage only at high dose levels. No effects were observed to the kidney or spleen of any of the animals except in extreme doses. Lamson (10) found no liver or kidney necrosis in dogs with doses up to stomach capacity. The degree of absorption of the chemical was found to be directly related to the fat content of the intestinal tract. In a more recent study, rats were given oral doses of radioactive labeled perchloroethylene to observe metabolic pathways (11). The results showed that perchloroethylene was excreted predominately through the lungs with only 2 percent of the dose excreted in the urine. Table I shows the results of various other acute

oral toxicity studies.

Table I.

Acute oral toxicity values for perchloroethylene.

<u>Animal</u>	<u>Lethal Dose</u>	<u>Time of Death</u>	<u>Reference</u>
Cat	5 ml/kg		3
Cat	6.5 g/kg	6-36 hrs.	12
Cat	5 ml/kg (in milk or water)	24 hrs.	
Mouse	8.12 g/kg	2- 9 hrs.	12
Mouse	8.85 g/kg (LD ₅₀)		12
Mouse	4-5 ml/kg (LD ₅₀) (in peanut oil or peanut and castor oil)		7
Mouse	6 ml/kg (LD ₁₀₀) (in peanut oil or peanut and castor oil)		7
Rabbit	8.12 g/kg	7-20 hrs.	12
Dog	6.5 - 24.4 g/kg	7 1/2-72 hrs.	12

Perchloroethylene has a high vapor pressure, therefore, inhalation is a likely exposure route. Rowe, et al., as reported by Patty and Lamson (4,10), exposed rabbits, mice and rats to the vapors of perchloroethylene at amounts ranging from 2,000 to 12,000 ppm. At the higher levels of exposure, the predominant response was CNS depression. Other effects noted were slight changes in liver, weight and total lipid content. Repeated exposures of rats to 2,500 ppm were found to be lethal in 18 days. However, studies on other animals showed only CNS depression at the same dose level (3,4,10). No effects on the liver-lipid content were reported by Daniel (11) when rats were exposed to 1,000 ppm of perchloroethylene vapor.

Mice were used in another study to determine the hepatotoxic potency of perchloroethylene. A change in the level of a liver enzyme was used to measure the hepatotoxicity 24 hours after a single vapor exposure of 3,200 ppm, however, this concentration provided sufficient dose to cause death (14). Table II shows the results of other controlled inhalation studies conducted on animals.

Table II.

Acute inhalation toxicity values for perchloroethylene.

<u>Animal</u>	<u>Lethal Concentration (ppm)</u>	<u>Exposure Time</u>	<u>Reference</u>
Mouse	7,800 (MLC)*	2 hours	12
Guinea Pig (old)	37,200	40 minutes	12
Guinea Pig (young)	37,200	9-12 minutes	12
Rabbit	5,500 (LD ₅₀)	-----	3

*Smallest concentration required to kill one test animal.

Other acute toxicity studies on perchloroethylene involved inter-peritoneal injection into dogs to observe effects on liver and kidney function. Perchloroethylene was found to have an LD₅₀ of 2.1 ml/kg in a vehicle of corn oil (15). At near lethal doses, an elevation in the liver enzyme used to measure toxicity was noted as well as slight cellular changes but with no necrosis histopathologically. Perchloroethylene was found to cause some alteration in kidney function at 1.4 ml/kg. In another study with dogs, intravenous injection of 85 mg/kg (MLD) of perchloroethylene was found to be the smallest dose required to kill one of the dogs in the experimental group 30 minutes after injection (12). A subcutaneous injection of 2,200 mg/kg of perchloroethylene was found to be the MLD for rabbits 24 hours after injection (12).

V. Chronic Toxicity:

There are very few animal studies on the chronic effects of perchloroethylene. Lamson (10) fed doses of 2 ml/kg of perchloroethylene to dogs for several months with no observed effects histologically or functionally. Carpenter, as reported by Patty and Browning (3,4), exposed rats 8 hours a day, 5 days a week to perchloroethylene vapors for up to 7 months. At a concentration of 70 ppm no effects were observed while at 230 ppm and 470 ppm pathological changes were noted in the liver and kidneys. Several other animal species were subjected to long term vapor exposures. The first week exposure to 1,600 ppm resulted in rats showing a depressed and drowsy behavior with definite irritation observed some time after exposure was terminated. The liver and kidneys had enlarged noticeably in these animals. Guinea pigs showed an increase in liver and kidney weight and a slight fatty degeneration of the liver. Rabbits and monkeys at this dose level, showed no observable effects. At a vapor exposure of 200 ppm, guinea pigs exhibited an increase in liver weight while at an exposure of 100 ppm no histopathological changes were observed.

The animal data available on perchloroethylene's chronic effects show it to be toxic at moderate exposure levels resulting in possible liver and kidney damage as well as other systemic changes.

VI. Human Toxicity:

Perchloroethylene has been the drug of choice for 40 years in treating hookworm infections, specifically those involving Necator americanus and Ancylostoma duodenale infections (16). Studies on over 50,000 patients infected with N. americanus have shown this chemical to be safe and effective at single oral doses of 5.0 ml. The low toxicity of perchloroethylene, when administered in therapeutic doses, has been attributed to

the nonabsorption of the drug in the intestinal tract in the absence of alcohol or fats (7,16). Liver function tests on patients so treated have been normal, the only side effects being occasional nausea, vomiting, giddiness, mild inebriation and in 2 cases a temporary loss of consciousness (16). Symptoms ordinarily disappear in a short time but circulatory collapse and death has been reported in those patients that were highly emaciated (6).

Primarily, the acute data on perchloroethylene intoxication has come from cases involving industrial accidents or misuse of the chemical in coin-operated drug cleaning operations. Acute over-exposure to the vapors of this chemical may result in hepatic injury or anesthetic death (19). A number of cases of fatal CNS depression have been reported from the use of such items as sleeping bags which were not completely aired of the perchloroethylene used as a dry cleaning solvent (5). Exposure to the vapors of perchloroethylene is the most common means of contact to this chemical in industry. It is suggested that physical examinations of occupationally exposed persons be conducted annually and include studies of the liver and kidney. Those workers with diseases of the heart, liver, kidney or lungs should be precluded from any job involving exposure to perchloroethylene. The vapors of this chemical are readily absorbed by the lungs, nose and throat and can be irritating at high concentrations to the eyes causing lacrimation and burning (4,5). When humans were experimentally exposed to 106 ppm, slight dizziness and some sleepiness was noted while at 280 ppm the subjects complained of light headedness, irritation of the eyes and definite motor coordination impairment. The exposures were assumed to be single dose exposures although the source did not mention the duration. Other acute inhalation experiments with humans have shown effects ranging from a slight narcosis after a 5 minute exposure to 2,000 ppm of

perchloroethylene to slight coordination impairment after 10 minutes of exposure ranging from 513 ppm to 690 ppm of the vapors with recovery observed in one hour (7). After a 2 hour exposure to 206 ppm to 356 ppm of perchloroethylene, symptoms, such as eye burning, sinus congestion, a thick tongue, impaired coordination and nausea, were all reported with recovery in one hour. Acute vapor exposure to perchloroethylene was again studied using human male volunteers for periods ranging from 1 to 3 hours (20). The concentrations of perchloroethylene ranged from 75 ppm to 244 ppm. Subsequently, the amounts of the chemical were measured in both the blood and expired air. The expired air was found to contain sufficient perchloroethylene to estimate the level of exposure several hours after exposure had occurred. The concentration of perchloroethylene in the expired air was found to be related to several factors in a later study by the same author (18). These factors were: (1) the total amount of perchloroethylene absorbed through the lungs, skin or gastro-intestinal tract, (2) duration of exposure, (3) the time lapse after exposure, (4) the rate of excretion of the chemical from the lungs during and after the exposure, (5) the whole blood concentration and (6) the total body-lipid storage. It was discovered that the compound was metabolized and stored in tissues with a high lipid content in minute amounts and poorly absorbed by the skin unless trapped there by an impermeable layer. Others have suggested that a small amount of the chemical may be converted into a water soluble metabolite (4). The physiological effects observed in the human volunteers were very slight eye irritation at 75 ppm to 80 ppm to slight light headedness at 210 to 244 ppm (20). Stewart (18) reported a case of acute industrial intoxication with perchloroethylene which resulted in a narcotic effect and transient liver injury. A workman wearing a chemical respirator entered a tank car to clean it with perchloroethylene.

The vapors filled the mask and caused him to lose consciousness. After 1 1/2 hours from the time of exposure his breath contained 105 ppm. He was drowsy but had no other symptoms. Two days later he complained of slight fatigue and liver function tests showed slight liver injury.

Chronic exposure to perchloroethylene at relatively low vapor concentrations may cause liver and kidney damage (4,19). Coler and Ross-miller, as reported by Patty (4), disclosed 7 cases of industrial exposure ranging from 232 ppm to 385 ppm. One of the cases had severe gastric hemorrhage and cirrhosis of the liver while the other 6 were observed to have headaches, nausea, light headedness, dizziness, fatigue, feelings of intoxication and hangover. Three of the six were shown to have liver dysfunctions, two had altered serum protein patterns and one had a 3+ cephalin cholesterol reaction. Another chronic exposure case resulted in a semi-comatose state and mild liver injury for a man exposed to 400 ppm of perchloroethylene for 3 hours (19). Stewart (19) used humans to test chronic exposures to perchloroethylene at a 7 hour exposure for 5 consecutive days with concentrations ranging from 96 ppm to 109 ppm. After a 5 minute exposure the odor was described as being strong, however, the odor was noticed less and less as time wore on until after 5 days it was not noticed at all. The initial 7 hour exposure to perchloroethylene vapors resulted in a variety of experiences including lightheadedness, chest discomfort, abdominal pain, speech difficulties and eye, nose and throat irritation. Those exposed for 5 days had fewer complaints as each day passed. One experiment exposed the subjects to 3 hours of 100 ppm perchloroethylene resulting in motor impairment in three persons.

It appears that while acute exposure to perchloroethylene has adverse effects only at high concentrations, chronic exposure to concentrations even lower than those of the threshold limit value may be injurious.

VII. Environmental Toxicology:

There is little information of the effects of perchloroethylene upon the environment. Sax (21) describes perchloroethylene as being extremely stable and resisting hydrolysis. This chemical is non-explosive and non-flammable but if heated to decomposition it will produce chloride gases which are highly toxic (4,21). Perchloroethylene has been used as an insecticidal fumigant and as a fungicide in agriculture (7,8). To date there have been no studies on environmental accumulation, biodegradation or ecosystem effects.

VIII. Recommendations:

Perchloroethylene has a high vapor pressure, therefore, exposure most often occurs by inhalation of the vapors. The acute toxicity values for perchloroethylene suggest that only at very high dose levels, either orally or when inhaled, this chemical may be a serious health hazard, however, the chronic data indicates that moderate vapor concentrations over a period of time can cause liver and kidney damage and may even be fatal. There have been no studies showing a carcinogenic effect although a closely related chemical, trichlorethylene, is a suspected carcinogen.

Considering the toxic nature of perchloroethylene, it is recommended for use in solar energy heating and cooling units if extreme caution is taken to avoid human exposures, especially via the respiratory route.

References

1. National Institute for Occupational Safety and Health. 1975. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
2. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Co., Cleveland, Ohio.
3. Browning, Ethel. 1965. Toxicity and Metabolism of Industrial Solvents. Elsevier Publishing Company. New York.
4. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers, John Wiley and Sons, Inc. New York.
5. Hamilton, A. and Hardy, H.L. Industrial Toxicology. Publishing Science Group, Inc. Action, Massachusetts. 1974.
6. Lefaux, René. Practical Toxicology of Plastics. Iliffe Books Ltd. London, England. 1968.
7. National Academy of Sciences. 1959. Handbook of Toxicology. Vol. III. Insecticides.
8. National Academy of Sciences. 1959. Handbook of Toxicology. Vol. V. Fungicides.
9. Schlingman, A.S. and O.M. Gruhzt. 1927. Studies on the Toxicity of Tetrachloroethylene, A New Anthelmintic. Am. Vet. Med. Assoc. 71: 189-209.
10. Lamson, P.D. 1929. The Pharmacology and Toxicology of Tetrachloroethylene. Am. J. of Hygiene. 9: 430-444.
11. Daniel, J.W. 1963. The Metabolism of ³⁶Cl-Labeled Trichloroethylene and Tetrachloroethylene in the Rat. Bio. Pharm. 12: 795-802.
12. National Academy of Sciences. 1959. Handbook of Toxicology. Vol. I. Acute Toxicities.
13. American Conference of Governmental Industrial Hygiene. 1974. Documentation of the Threshold Limit Values. 3rd edition. Cincinnati, Ohio.
14. Gehring, P.J. 1968. Hepatotoxic Potency of Various Chlorinated Hydrocarbon Vapors Relative to their Narcotic and Lethal Potencies in Mice. App. Pharm. 13: 287-298.
15. Klassen, Curtis and Gabriel Plaa. 1966. Relative Effects of Various Chlorinated Hydrocarbons on Liver and Kidney Function in Mice. Tox. and App. Pharm. 9: 139-151.

16. Brown, Harold. 1969. Anthelmintics, Old and New. Clin. Pharm. and Therap. 10: 5-29.
17. Plunkett, E.R. 1966. Handbook of Industrial Toxicology. Chemical Publishing Company, Inc. New York.
18. Stewart, Richard. 1969. Acute Tetrachloroethylene Intoxification. JAMA. 208: 1490-1492.
19. Stewart, Richard. 1970. Experimental Human Exposure to Tetrachloroethylene. Arch. of Env. Health. 20: 224-229.
20. Stewart, Richard. 1961. Human Exposure to Tetrachloroethylene Vapor. Arch. of Env. Health. 2: 40-46.
21. Sax, Irving. 1975. Dangerous Properties of Industrial Materials. Van Nostrand - Reinhold Company.

TOXICOLOGICAL EVALUATION OF 1,1,2 - TRICHLOROETHANE

July 21, 1976

ABSTRACT

1,1,2 - Trichloroethane (TCE) is a member of the large chemical family known as the halogenated aliphatic hydrocarbons. Unlike other chemicals in this family that have wide industrial application as solvents, TCE had not developed significant industrial usage as late as 1967. From an acute standpoint, TCE displays a relatively high order of toxicity. Although its major acute physiological effect is depression of the central nervous system, TCE can irritate the eyes, skin, respiratory membranes, and intestinal tract, potentiate adrenalin, cause severe liver and kidney dysfunction and damage, and cause death. Acutely toxic doses of TCE can be obtained through all major routes of exposure. The chronic toxicity of TCE is believed to be quantitatively and qualitatively comparable to carbon tetrachloride. The environmental and industrial toxicologies of the compound are not known.

On the basis of toxicological information currently available, 1,1,2 - trichloroethane is not recommended for use as a heat exchange medium for solar cooling and heating.

I. Chemical Properties:

Name: 1,1,2 - Trichloroethane

Molecular Formula: $\text{CHCl}_2\text{CH}_2\text{Cl}$

Molecular Weight: 133.41 (1)

Synonyms: Vinyl trichloride; beta - trichloroethane; ethane
trichloride; 1,1,2 - trichlorethane; trojchloroetan (1,1,2)
(Polish) (2)

Freezing Point: -31°F Boiling Point: 237°F , 113.77°C (1)

Flash Point: None

Specific Gravity: 1.443 ($20^{\circ}/4^{\circ}\text{C}$) (3)Refractive Index: $n_D = 1.4714$ @ 20°C (1)

Vapor Density: 4.6 (air = 1) (3)

Vapor Pressure: 25 mm Hg @ 25°C (3)Percent in Saturated Air: 3.3 @ 25°C (3)

Density of Saturated Air: 1.1 (air = 1) (3)

Solubility: 0.44 g in 100 g water @ 20°C (3)

Soluble in all proportions in alcohol, ether, and chloroform (1)

Physical State: Sweet smelling, colorless liquid (3)

At 25°C and 760 mm Hg: 1 ppm = 5.46 mg/cu. meter

1 mg/liter = 183 ppm (3)

II. Hygienic Standards:

TLV: Air 10 ppm (Approximately 45 mg/m^3) (OSHA Standard 1910.93)

This chemical is also absorbed through the skin.

III. General Toxicology:

1,1,2 - Trichloroethane (TCE) is a member of a large family of chemical compounds known as the halogenated aliphatic hydrocarbons. This group of compounds, in particular the chlorinated aliphatic hydrocarbons, have an almost universal application in industry because of their excellent solvent properties (3,4). TCE has been produced since 1828 by the action of vinyl chloride on antimony perchloride. It has found use since then as a chemical intermediate and as a solvent, but unlike other chlorinated aliphatic hydrocarbons, as late as 1967, significant industrial usage of TCE had not developed (4).

The compounds belonging to this chemical family display a wide range of toxicological properties. The halogenated aliphatic hydrocarbons are generally more active than the corresponding unsubstituted hydrocarbons, with degree of toxic action varying with the number of carbon atoms in the chain, number of double bonds between carbon atoms, and the degree of halogenation (5). The most common physiological response, that is characteristic of all halogenated aliphatic hydrocarbons is narcosis. However, the effect may vary in degree from deep anesthesia to only weak narcosis or inebriation (3,4). Following narcosis, the most significant qualitative toxic response to halogenated aliphatic hydrocarbons is liver and/or kidney injury. Being quite volatile, these compounds pass through the body with little metabolic change, but many will react with enzymes in the liver and kidney, causing complete

disorganization of enzyme balance and subsequent damage to the organs (4). Two other physiological responses are usually characteristic of compounds in this chemical family. At least some degree of respiratory irritation is normally visible, and most of the chemicals are known to potentiate adrenalin, some in quantities large enough to cause cardiac arrhythmia in cases of severe acute poisoning (3).

TCE exhibits all of the toxicological phenomenon characteristics to the halogenated aliphatic hydrocarbons. Its principal physiological effect is depression of the central nervous system. The anesthetic and narcotic actions of this compound are greater than those of the 1,1,1 - isomer and considerably more potent than those of chloroform (6). TCE has a marked capacity for injury to the liver, and to a certain extent, the kidneys. Toxic doses of TCE can be obtained through any route of exposure, since it is readily absorbed through the lungs, intestinal tract, and intact skin (5). Irritation of the gastrointestinal tract, eyes, and nose result from exposure to narcotic concentrations of TCE, and although not conclusively proven, its ability to potentiate adrenalin is suspected (4,5,7).

IV. Acute Toxicity:

There is much data available on the acute toxicity of TCE, especially in conjunction with its ability to cause damage to the liver and kidneys. In terms of relative toxicity, TCE has been measured to be 3.3 times as acutely toxic as chloroform (5). The LD₅₀ values for TCE have been established for all of the major routes of exposure, however, all of the available data is for animals since none has been generated for man. The LD values for TCE are summarized in Table I. The values

indicate that TCE displays a fairly high order of acute toxicity from all routes of exposure, the exception being fatality caused by inhalation of TCE vapor which requires rather high concentrations. The LD₅₀ value for dermal exposure also indicates the rapidity and ease with which TCE is absorbed through intact skin, since the value was tabulated from lethality caused in a 24 hour period after application of the chemical.

TABLE 1.

Acute Toxicity Data for 1,1,2 - Trichloroethane

<u>Route of Exposure</u>	<u>Animal</u>	<u>LD₅₀</u>	<u>LC₅₀</u>	<u>Reference</u>
Oral	Dog	0.5 ml/kg	----	8
	Dog	0.75 g/kg	----	5
	Rat	0.2 g/kg	----	3
	Rat	1.14 g/kg	----	9
	Rat	0.58 g/kg	----	2
Subcutaneous	Mouse	1.7 mmole/kg	----	10
	Rabbit	0.5 g/kg	----	5
Intravenous	Dog	95 mg/kg	----	5
Inhalation	Mouse	----	11,000 ppm/2 hrs.	5
	Rat	----	2,000 ppm/4 hrs.	4
	Rat	----	500 ppm/8 hrs.	9
Dermal	Rabbit	3.73 ml/kg	----	9
Intraperitoneal	Mouse	0.35 ml/kg	----	11
	Mouse	3.7 mmole/kg	----	12
	Dog	0.45 ml/kg	----	13

Although the ability of TCE to cause death from acute exposure is a concern, more attention has been given to the narcotic, hepatotoxic, and nephrotoxic potentials of the chemical. It has been estimated that doses approximately equal to one-fourth of the lethal concentration will cause narcosis. In animals, narcosis, induced by inhalation of TCE, is usually preceded by a stage of excitation followed in 3 to 7 minutes by complete anesthesia without marked effects on respiratory rate, pulse rate, and blood pressure. At higher concentrations or extended periods of exposure, cerebral irritation may occur followed by death from respiratory arrest (4,5,6,8). In man, narcosis appears in 15 to 20 minutes after inhalation of TCE and is accompanied by increased pulse rate and salivation (8). If narcotic doses are administered orally, severe irritation of the intestinal tract results in a gastroenteritis characterized by salivation, nausea, vomiting and diarrhea. In the most severe cases, the gastric mucosa can become severely inflamed and haemorrhage of the caecum and colon may occur (4). Narcotic doses of TCE also cause irritation of the skin, eyes, respiratory membranes (5,9).

Much research has been done recently on the hepatotoxic and nephrotoxic capabilities of TCE. Repeated experiments have shown that narcotic doses of the chemical can cause liver and kidney dysfunction in the laboratory animals (10,11,12,13,14). The hepatotoxicity of TCE is of a fairly high order, and although its nephrotoxic effects are not as marked, considerable damage can result to the kidneys from intoxication. The potential that TCE possesses to produce liver dysfunction in mice and dogs from acute exposure is not as great as the potential of carbon tetrachloride and chloroform, but TCE is still considered a potent hepatotoxin (10,12). Narcotic doses, delivered intraperitoneally or by inhalation, cause

liver dysfunction that will continue for a period of 7 to 10 days, after which liver function will return to normal (13). However, the liver remains damaged, showing histological changes consisting of passive congestion, advanced cloudy swelling, fatty degeneration, and central necrosis (8). Although TCE does not have nephrotoxic capabilities equal to its hepatotoxic potential, kidney dysfunction has been induced in mice and dogs from acute exposure approximately equal to narcotic dosages of TCE (11,13,14). Interperitoneal injection of TCE produces immediate nephrotoxicity, with kidney dysfunction lasting for a period of one day before normal kidney function resumes (14). Like the liver, however, the kidney displays histological changes after return to normal function of cloudy swelling, necrosis with karyolysis, and loss of epithelium of the convoluted tubules (8,11).

In conclusion, TCE holds a relatively high order of acute toxicity. Toxic doses of TCE can be reached from exposure by any of the major entry routes. The acute toxic effects of this compound cover a wide range of physiological response, including irritation of the skin, eyes, respiratory membranes, and intestinal tract, potentiation of adrenalin, narcosis, hepatotoxicity, nephrotoxicity, and lethality. It should be noted that available toxicological data on TCE pertains only to laboratory animals since there are no reports of human poisoning from acute exposure to TCE.

V. Chronic Toxicity:

The toxic effects of chronic exposure to TCE are not known. No long-term toxicity studies on TCE are currently available for animals or man. However, unpublished animal investigations cited by Patty (3) indicate that the toxicological response from chronic exposure to TCE

would be qualitatively and quantitatively comparable to carbon tetrachloride. Carbon tetrachloride is a potent hepatotoxic and nephrotoxic agent, able to cause severe damage from long-term exposure at sub-acute levels (3,6). In addition, the American Conference of Governmental Industrial Hygienists, recommended a low TLV of 10 ppm for TCE because of its great toxicological resemblance to symmetric tetrachloroethane, a compound proven more toxic than carbon tetrachloride by both industrial experience and toxicologic experiments (6).

VI. Environmental Toxicology:

The action of TCE in the environment is not known. Data assessing the biodegradability and food chain transport mechanisms of this compound is not currently available. An aquatic toxicity rating has been assigned to TCE by the 1975 Registry of Toxic Effects of Chemical Substances. A TL_{m96} value ranging from 100 ppm to 10 ppm is given to the chemical. This is the concentration range of TCE which will kill 50 percent of exposed aquatic test organisms in 96 hours, and can be interpreted to mean that TCE is only slightly toxic to aquatic life (2).

The toxicology of TCE in the industrial environment is also unknown. Since this chemical had not developed significant industrial usage as late as 1967, exposure data of workers to TCE does not exist. There are indications that TCE is used more widely today as a solvent than in previous years. Even though the assigned TLV of 10 ppm should be sufficient to prevent physiological effects, good industrial hygiene practices should be used when working with TCE. Work areas should be adequately ventilated, and workers should be supplied with chemical cartridge respirators, goggles, and rubber gloves. Exposed personnel should receive physical examinations and individuals with diseases of the liver and kidneys should not be

allowed to work with the compound (7).

VII. Recommendations:

On the basis of toxicological information currently available, 1,1,2 - trichloroethane is not recommended for use as a heat exchange medium for solar heating and cooling. The ability of TCE to be acutely toxic from all major routes of exposure, plus the many different physiological responses that it may induce, make this chemical unsuitable for use in a heating and cooling unit that may find widespread private and commercial use. In addition, the unknown chronic, environmental, and industrial toxicologies of this compound should be known before widespread public use of TCE as a heat exchange medium could be considered. If TCE is acceptable as a heat exchange medium based on other experimental criteria, consideration of the 1,1,1 - isomer would be toxicologically more suitable, since this compound seems to be considerably less toxic than the 1,1,2 - isomer currently under consideration.

References

1. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
2. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
3. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers. John Wiley and Sons, Inc. New York. 1967.
4. Browning, E. Toxicity and Metabolism of Industrial Solvents. Elsevier Publishing Company. Amsterdam. 1965.
5. von Oettingen, W.F. The Halogenated Hydrocarbons; Toxicity and Potential Dangers. Public Health Service Publication No. 414. U.S. Government Printing Office. Washington, D.C. 1955.
6. American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values. Third Edition. Cincinnati, Ohio. 1974.
7. Plunkett, E.R. Handbook of Industrial Toxicology. Chemical Publishing Company, Inc. New York. 1966.
8. Wright, W.H. and J.M. Schaffer. Critical Anthelmintic Tests of Chlorinated Alkyl Hydrocarbons and a Correlation Between the Anthelmintic Efficacy, Chemical Structure and Physical Properties. American Journal of Hygiene. Vol. 16. No. 2. pp. 325-428. September, 1932.
9. Deichmann, W.B. and H.W. Gerarde. Symptomatology and Therapy of Toxicological Emergencies. Academic Press. New York. 1964.
10. Plaa, G.L., et al. Relative Hepatotoxicity of Seven Halogenated Hydrocarbons. Journal of Pharmacology and Experimental Therapeutics. Vol. 123. pp. 224-229. 1958.
11. Klaassen, C.D. and G.L. Plaa. Relative Effects of Various Chlorinated Hydrocarbons and Liver and Kidney Function in Mice. Toxicology and Applied Pharmacology. Vol. 9. pp. 139-151. 1966.
12. Gehring, P.J. Hepatotoxic Potency of Various Chlorinated Hydrocarbon Vapors Relative to Their Narcotic and Lethal Potencies in Mice. Toxicology and Applied Pharmacology. Vol. 13. pp. 287-298. 1968.
13. Klaassen, C.D. and G.L. Plaa. Relative Effects of Various Chlorinated Hydrocarbons on Liver and Kidney Function in Dogs. Toxicology and Applied Pharmacology. Vol. 10. pp. 119-131. 1967.
14. Watrous, W.M. and G.L. Plaa. The Nephrotoxicity of Single and Multiple Doses of Aliphatic Chlorinated Hydrocarbon Solvents in Male Mice. Toxicology and Applied Pharmacology. Vol. 23. pp. 640-649. 1972.

TOXICOLOGICAL EVALUATION OF BENZYL CHLORIDE

April 21, 1976

ABSTRACT

Benzyl chloride is reported to be an intensely irritating chemical to the skin and mucous membranes of the eyes, nose, throat, lungs and gastrointestinal tract. Neoplasticity has been reported but only at very high, prolonged doses of exposure. A threshold limit value of 1ppm has been set primarily on the basis of the irritating qualities of the chemical. In view of the limited amount of toxicological data available and the low threshold limit value, benzyl chloride is not recommended for use in solar energy heating and cooling units.

I. Chemical Properties

Name: Benzyl Chloride

Molecular Formula: $C_6H_5CH_2Cl$

Molecular weight (1): 126.59

Synonymus (1): alpha-Chlorotoluene; Benzile (Cloruro Di) (Italian);

Benzyle (Chlorure De) (French); Benzyl Chlorid (German);

alpha-Chlorotoluol (German); Chlorure De Benzyle (French).

Melting point (2): -43° C.

Boiling point: 354° F.

Freezing point: -45° F.

Flash point: 153° F.

Autoignition point: 1085° F.

Specific gravity: 1.1

Vapor density (3): 4.36

Lower explosive limit (3): 1.1%

Solubility (2): Water-Insoluble Alcohol-miscible Ether-
miscible Chloroform-miscible

Appearance (3); Colorless liquid, very refractive

Odor (4): When heated to decomposition it forms phosgene

II. Hygenic Standards

TLV: 1 ppm (approximately 5 mg/m^3) (OSHA standard 1910.93)

III. Background

Benzyl chloride is one of many halogenated hydrocarbons. The diverse physiological response to these different compounds makes it exceedingly difficult to generalize on their toxicity (5). Since several of these compounds potentiate adrenalin, it should not be given to a person after exposure to a halogenated hydrocarbon unless that specific compound is known not to cause this effect.

Exposure to benzyl chloride can occur in such occupations as photography, chemical synthesis, pharmaceutical preparation, leather tanning, dye, perfume and resin preparation (4). In the 1960's approximately 21 million pounds of benzyl chloride were used in the preparation of benzyl alcohol and related esters (6).

IV. Acute and Chronic Toxicity

Although the vapor pressure is assumed to be low for benzyl chloride, it is reported as being a potent lacrimator and extremely irritating to the skin, eyes, and mucous membranes (7, 8). Benzyl chloride, being an irritant, has the capability of causing lung edema and pneumonitis (9). It is a skin sensitizer and may cause skin burns (4).

First aid involves flushing the exposed area with water for 15 minutes, treating the burns as usual and taking medical precautions to insure against eye damage (4, 7, 8). If ingested, benzyl chloride is very irritating and vomiting or gastric lavage should be induced followed by saline catharsis (4, 8).

The threshold limit value of 1 ppm is based primarily on benzyl chloride's irritating properties as determined by ACGIH and accepted by OSHA (7).

The sources listed by NIOSH, in the Registry of Toxic Effects, have reported the results seen in Table I (1).

TABLE I
Acute and chronic toxicity data for
benzyl chloride

Animal	Route of exposure	LD ₅₀ (mg/kg)
Rat	oral	1231
Mouse	oral	1624
Rat	subcutaneous	1000
Rat	subcutaneous	*TDLo: 2100

*Lowest dosage given that caused neoplastic effects, administered over 51 weeks intermittently in a number of separate and discrete doses.

The high dose levels at which the above animals were subjected shows benzyl chloride to be relatively harmless if taken orally or subcutaneously. In contrast the inhalation of benzyl chloride is extremely toxic and can result in serious injury. At 16 ppm benzyl chloride is reported as being intolerable for humans (9).

Sax lists benzyl chloride as having a toxicity rating of 3 for both acute local and systemic exposures (3). This severe toxicity rating means that if benzyl chloride is locally applied, ingested or inhaled or is introduced systemically by skin absorption, ingestion or inhalation as just a single exposure of short duration, it can cause a severe enough injury to be life threatening or disabling, however, in industrial exposures no effects have been reported (4). No valid data

exists for the effects of benzyl chloride at chronic local or systemic exposures (3).

V. Environmental Toxicology

When benzyl chloride is heated to decomposition it forms phosgene (4). The possibility of explosion due to rapid decomposition exists if the chemical is used in association with hot metals such as iron (e.g. welding) (3). Sax lists benzyl chloride as being a dangerous disaster hazard since in the presence of H₂O or steam, toxic and corrosive fumes are produced (3). Considering the use for which this chemical is intended the risk of this hazard occurring is extremely high. Benzyl chloride can also react vigorously with oxidizing materials (3).

On the basis of toxicity to aquatic life benzyl chloride was found to be moderately toxic (1). Aquatic organisms were tested at various concentrations of benzyl chloride until a concentration of 1-10 mg/l was determined that would kill 50% of the test organisms within 96 hours.

VI. Recommendations

With the information available, benzyl chloride appears to be very irritating and potentially dangerous to those occupying homes which contain the chemical in solar energy units. The scarcity of data concerning human or animal exposure to benzyl chloride makes it difficult to evaluate in terms of chronic effects. With the present limited information regarding acute toxicity benzyl chloride is not recommended for use in solar energy or cooling units.

REFERENCES

1. National Institute for Occupational Safety and Health. 1975. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
2. Weast, R. 1972. Handbook of Chemistry and Physics. Chemical Rubber Co., Cleveland, Ohio.
3. Sax, Irving N. 1975. Dangerous Properties of Industrial Materials. Van Nostrand-Rheinholdt Co.
4. Plunkett, E. R. 1966. Handbook of Industrial Toxicology. Chemical Publishing Co.
5. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers, John Wiley and Sons, Inc. New York.
6. Sconce, J. S. 1962. Chlorine. Its Manufacture, Properties and Uses. Reinholdt Publishing Corporation, New York.
7. American Conference of Governmental Industrial Hygienists. 1974. Documentation of the Threshold Limit Values. Cincinnati, Ohio.
8. Deichman, Wm. and Horace Gerade. 1964. Symptomology and Therapy of Toxicological Emergencies. Academic Press, New York.
9. Smuth, H. F. 1956. Hygienic Standards for Daily Inhalation. Am. Ind. Hyg. Assn. Quart. 17:129.

TOXICOLOGICAL EVALUATION OF THERMINOL 55

September 10, 1976

ABSTRACT

Therminol 55 is the trade name given to a relatively new chemical conglomerate manufactured by Monsanto Company for use specifically as a heat transfer agent. Because the specific formulation of the compound is regarded as a proprietary secret, it can be toxicologically evaluated only as a mixture of alkylated benzenes. In general, the alkylbenzenes are classified as moderately toxic compounds, possessing the ability to cause central nervous system depression and primary irritation of the respiratory tract, eyes, and skin. The most toxic of the alkylbenzenes can cause pneumonitis of the lungs and a dermatitis of the skin. The alkylbenzenes do not, however, attack the blood forming tissues like their parent compound benzene. The only specific toxicological data that is currently available for Therminol 55 has been generated by Monsanto. Their results indicate that Therminol 55 is apparently a toxic agent of low grade from both acute and chronic exposure. The environmental and industrial toxicologies of the compound are not known.

On the basis of toxicological information currently available, Therminol 55 is not recommended for use as a heat exchange medium for solar heating and cooling. Although the toxicological data supplied by Monsanto indicates that Therminol 55 is relatively nontoxic, its specific formulation is currently not available making it impossible to evaluate the toxicology of its several components. Until Therminol 55 can be toxicologically evaluated by someone other than its sole manufacturer, use of a chemical that has been proven toxicologically safe by intense research should be given priority.

I. Chemical Properties:

Name: Therminol 55

Molecular formula (1): mixture of alkylated benzenes.

Freezing point: -20°F

Boiling point: 410°F

Flash point: 355°F

Auto-ignition point: 675°F

Specific gravity: 0.8867

Viscosity (centipoises) (1): 1,610 @ 0°F; 30.1 @ 100°F; 5 @ 200°F;
2.1 @ 300°F

Vapor pressure (1): <1 mm Hg @ 20°C

Solubility (1): negligible in water

Physical state (1): essentially odorless, clear, yellow liquid

II. Hygienic Standards:

There are presently no available standards for exposure to Therminol 55.

III. General Toxicology:

Therminol 55 is the trade name given to a relatively new chemical conglomerate that is formulated, manufactured, and marketed solely by the Monsanto Industrial Chemical Company. Therminol 55 is just one of a series of Therminol compounds that are custom blended by Monsanto for use as heat transfer agents. Because the specific composition of Therminol 55 is regarded as a proprietary secret, the chemicals used to formulate the compound and the percentages in which they appear are unavailable at this time. Monsanto describes Therminol 55 only as a mixture of alkylated benzenes, a class of industrially important chemical compounds most widely

recognized for their excellent solvent properties. For these reasons, there is no mention of Therminol 55 in toxicological literature. The only data concerning the toxic potential of the compound that is currently available is that generated by Monsanto. However, some generalizations can be made about the toxicology of the alkylated benzenes as a group.

In general, the liquid alkylated benzenes can be classified as central nervous system depressants and primary irritants (2). Experience with these chemicals indicates that they are moderately toxic by inhalation, and moderately to slightly toxic by oral and dermal routes of acute exposure. When orally ingested in large amounts, the most common physiological response is irritation of the gastrointestinal tract, and although this is of concern, more attention has been given to the respiratory and dermal routes of exposure. Inhalation of alkylbenzene vapors leads to two toxic responses. The first is central nervous system depression. Alkylbenzenes have a particular affinity for nervous tissue because of their high lipid content. Once concentrated in sufficient amounts, the alkylbenzenes cause a syndrome characterized by sluggishness, stupor, anesthesia, blurred vision, narcosis, and coma (2). With large enough doses, permanent damage may occur, especially to the brain. The second effect of inhalation of alkylbenzene vapor is severe irritation of the mucous membranes and pulmonary tissue. Contact of the vapor with mucous membranes causes local irritation and vasodilation that will subside rather quickly. However, aspiration of small volumes of alkylbenzene into the lungs can cause severe damage. Because of their low surface tension, alkylbenzenes spread over large areas of the lung causing a pneumonitis characterized by pulmonary edema, hemorrhage, and tissue necrosis. Damage can be permanent and death may occur from respiratory paralysis (2).

The irritant potential of the alkylated benzenes is also exhibited upon contact of the chemicals with the eyes and the skin. Ocular exposure to alkylbenzenes causes itching, lacrimation, and irritation that can result in tissue injury with prolonged exposure (2). Dermal acute exposure to alkylated benzenes produces vasodilation, erythema, and irritation of short duration. Long term exposure results in a dermatitis caused by removal of natural cutaneous fats that leave the skin dried, scaled, and fissured (2). However, alkylbenzenes are only slowly absorbed through the skin, making systemic intoxication improbable from dermal exposure.

The effects of chronic exposure to alkylated benzenes are generally the same as those from acute exposure; central nervous system depression and primary irritation of the respiratory tract, eyes, and skin. Although alkylbenzenes have been suspected of attacking blood-forming tissues like their parent compound benzene, extensive animal experimentation indicates that they possess no myelotoxic potential. For this reason, it has been proposed that the alkylbenzenes be referred to as "phenylalkanes" to dissociate them from the more toxic benzene (3). In conclusion, the toxic potential of the alkylated benzenes is closely tied to chemical structure. The relative toxicity of an alkylated benzene depends on its water solubility, the number of alkyl groups on the benzene ring, and the length of the side chains (2). The toxic potential of the alkylbenzenes decreases as water solubility decreases, number of alkyl groups increases, and the length of the side chain decreases.

IV. Acute Toxicity:

The Monsanto Company has evaluated the acute toxic potential of Therminol 55. In their investigation, an oral LD₅₀ value was determined for rats of 15.8 g/kg. A dermal LD₅₀ for rabbits was also established at

7.94 g/kg (4). The ability of Therminol 55 to act as a primary irritant was also tested. The undiluted product is described as a slight irritant to rabbit skin, but practically nonirritating to the eye. In addition, reaction to acute respiratory exposure to Therminol 55 was evaluated. Male rats survived a 6 hour exposure to air near saturation with Therminol 55 vapor without apparent adverse effect (4).

The data generated by Monsanto would seem to indicate that their product is apparently a chemical with an extremely low order of acute toxicity.

V. Chronic Toxicity:

Data assessing the chronic toxicity of Therminol 55 is also available from Monsanto (4). A 90 day feeding study was completed with rats where daily exposure ranged from 100 ppm to 1,000 ppm. At the highest concentration, survival rate was normal, and macroscopic and microscopic examination of test animals revealed no significant differences when compared to controls. A similar 12 week oral exposure study was conducted with chickens at concentrations ranging from 30 ppm to 300 ppm daily intake. Again, survival rate was normal and there was no effect on reproduction or first generation birds. Monsanto's toxicological evaluation of Therminol 55 does not include data concerning the chronic toxicity of the chemical from the dermal and respiratory routes of exposure.

VI. Environmental Toxicology:

The action of Therminol 55 on the environment is not known. The biodegradability of the compound has not been studied, but Monsanto states that the spent fluid would act similar to crude oil and should be treated as such (4).

Because Therminol 55 is a relatively new industrial chemical, its toxicology in the working environment is not known. However, like other alkylated benzenes, Therminol 55 should be handled with care. It is essential to control respiratory exposure to alkylated benzenes with adequate ventilation at the source of vapor generation to prevent the induction of pneumonitis. In addition, the irritant properties exhibited by the alkylbenzenes can be controlled by use of goggles and impregnable rubber gloves.

VII. Recommendations:

In view of toxicological information currently available, Therminol 55 is not recommended for use as a heat exchange medium for solar heating and cooling. Although the toxicological data currently available from Monsanto indicates that Therminol 55 is relatively nontoxic, the chemical is a new compound with little industrial exposure. In addition, the specific formulation of Therminol 55 is currently protected as a proprietary secret, making it impossible at this time to detail the specific toxicology of its individual components. From experience with alkylated benzenes as a group, it is known that they have the potential to be quite toxic, and until Therminol 55 can be toxicologically evaluated by someone other than its sole manufacturer, use of a chemical that has been proven toxicologically safe by intense research should be given priority.

References

1. Monsanto Industrial Chemicals Company. Form No. OSHA-20. May, 1971.
2. Gerarde, H.W. Toxicology and Biochemistry of Aromatic Hydrocarbons. Elsevier Publishing Company. Amsterdam. 1960.
3. Patty, F.A. Industrial Hygiene and Toxicology; Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
4. Monsanto Industrial Chemicals Company. Therminol 55 Toxicity Statement. August, 1973.

TOXICOLOGICAL EVALUATION OF O-DICHLOROBENZENE

July 20, 1976

ABSTRACT

O-Dichlorobenzene (ODCB) is a chlorine derivative of benzene that belongs to the large chemical family of cyclic halogenated hydrocarbons. It is produced commercially in the United States in sizable quantities, and finds widespread industrial and agricultural use. Existing toxicological data on ODCB shows it to have a relatively low order of acute and chronic toxicity in animals and humans from all routes of exposure. The major toxicological effects of ODCB are irritant action on the eyes, skin, and respiratory tract, and damage to the liver and kidneys from long-term exposure. Fatal doses of ODCB are unlikely because of the large dose requirements for toxic effect and because the compound possesses good warning properties of exposure. There is some question of the ability of ODCB to cause cancer and of its ability to biodegrade in the environment. From an industrial hygiene standpoint ODCB has been proven relatively safe because its irritant properties usually dictate controls to safe levels of exposure. Perhaps the greatest area of concern is that of the safety of ODCB as a heat exchange medium. Its relatively low flash point creates the possibility of a fire hazard in a system that will operate at temperatures well above the chemical's flash point.

In view of the toxicological and safety information currently available, ODCB is recommended for use as a heat exchange medium for solar heating and cooling only with reservations as to its irritant qualities and fire potential.

I. Chemical Properties:

Name: O-Dichlorobenzene

Molecular formula: $C_6H_4Cl_2$

Synonyms: 1,2-dichlorobenzene; orthodichlorobenzol; o-dichlorobenzol; chloroben; cloroben; Dowthern E; Dizene; DCB, ODCB, ODB (1).

Molecular weight: 147.01 (2).

Freezing point: $-8^{\circ}F$.Boiling point: $356^{\circ}F$, $180.5^{\circ}C$ (2).

Specific gravity: 1.307.

Flash point: $151^{\circ}F$ (closed cup); $155^{\circ}F$ (open cup) (3).Auto-ignition point: $1,198^{\circ}F$.

Solubility: Insoluble in water, infinite in most organic solvents including alcohol, ether, benzene, acetone, and carbon tetrachloride (2,3,4,5).

Vapor pressure: 0.631 mm Hg @ $15^{\circ}C$; 1.282 mm Hg @ $25^{\circ}C$;10.0 mm Hg @ $59.6^{\circ}C$; 30.0 mm Hg @ $82.4^{\circ}C$; 100.0 mm Hg @ $112.4^{\circ}C$ (4).Refractive index: $N_D = 1.5515$ @ $20^{\circ}C$ (2).

Explosive limits: 2.2 to 9.2% in air (4).

Threshold of perception: 2 to 4 ppm for odor; 20 to 30 ppm for eye irritation (4).

At $25^{\circ}C$ and 760 mm Hg: Saturated air contains 0.17% by volume.

Relative density of saturated air: 1.007
(air = 1.000).

1 ppm = 0.00601 mg/liter.

1 mg/liter = 166.3 ppm (4).

Physical state: Colorless liquid (3).

II. Hygienic Standards:

TLV: air 50 ppm; 300 mg/m³ (OSHA Standard 1910.93)

III. General Toxicology:

O-Dichlorobenzene (ODCB) is a member of a large chemical family known as the cyclic halogenated hydrocarbons. It is produced commercially by chlorinating benzene or monochlorobenzene at 150-190°C in the presence of ferric chloride catalyst. The resulting mixture of ortho and para-dichlorobenzene can be separated into the two components by fractional distillation or by crystallization of the para-isomer (5). ODCB has been produced commercially in this manner since at least 1921. In 1972, United States production totaled 28 million kg and 1973 production was estimated to be between 32-41 million kg (5). Over the years, ODCB has found a variety of commercial applications. It has been used as a solvent for the removal of lead and carbonaceous deposits from engine parts; as a component in a rust-proofing mixture; as a heat exchange medium; as a magnetic coil coolant; as a dye intermediate; as a degreaser for leather, metals, and wool; as a component for metal polishes; as an insecticide; and for the desulphurization of illuminating gas (3,5). In 1973, the United States consumption pattern for ODCB was as follows: 53 percent for organic synthesis (chiefly pesticides), 20 percent as a

process solvent in toluene diisocyanate production, 15 percent in miscellaneous solvent uses, 8 percent in the manufacture of dyes, and 4 percent for miscellaneous uses (5).

In general, the aromatic halogenated hydrocarbons show a similar toxicology despite the diversity in their chemical structures. The primary physiological response to almost all of the aromatic halogenated hydrocarbons is injury to the liver and secondarily to the kidneys. Some of the members of this chemical family are also depressants of the central nervous system, giving them an anestheticlike action. Responses of this type are usually induced by exposure via the respiratory or oral routes. Dermal exposure to this class of compounds will produce an irritative response, ranging in degree from slight to severe. In addition, the chlorinated biphenyls and chlorinated naphthalenes are inducers of an occupational dermatitis known as chloracne. This syndrome is caused by the ability of these compounds to alter the differentiation of the sebaceous gland cells, so that keratinocytes form to plug the unit and create keratin containing cysts. Once chloracne has been contacted, it can take months for the skin to return to normal (3,6). Although ODCB is a suspect inducer of chloracne, the compound does not possess the ability to cause the severe cases seen after exposure to the chlorinated biphenyls and naphthalenes.

More specifically, the toxicity of the chlorine derivatives of benzene is believed to be closely related to structure. Substitution of chlorine in the benzene ring increases toxicity until two chlorine atoms are added. Further additions of chlorine then decrease the toxicity of the chlorinated benzenes. This then makes the dichlorobenzenes the most toxic of the chlorinated benzenes. In addition, the positioning of the chlorine radicals on the

benzene ring alters toxicity. The ortho configuration displays the highest order of toxicity. The structure of ODCB thus makes it the most toxic of the chlorinated benzenes (7).

IV. Acute Toxicity:

The acute toxicity of ODCB is generally considered to be low to moderate. Even though this compound is considered to be the most toxic of all chlorinated benzenes, damage to health from acute exposure to ODCB is usually slight. These conclusions are based on the findings of a 1937 study by Cameron, et al. (7) and a 1958 report filed by Hollingsworth, et al. (8). These two studies, although exclusively concerned with the toxicological properties of ODCB in animals, supply the bulk of reliable information on the toxicity of ODCB currently available.

Both Cameron (7) and Hollingsworth (8) have tested the acute toxic effects of ODCB via the respiratory route. Although relatively low concentrations of the compound are evident because of its strong odor and irritating action on eyes and the respiratory tract, ODCB vapors are only lethal at extremely high concentrations. Cameron (7) found that guinea pigs had to be submitted to concentrations of 800 ppm ODCB in air for twenty-four hours before a fatal response could be induced. Hollingsworth (8) reports similar results with rats, exposing them for seven hours at 977 ppm before producing fatality. Rats survived an exposure of 977 ppm for two hours, and 539 ppm for seven hours. When exposed at these high levels, animals show drowsiness, unsteadiness, and eye irritation. Even if this type of severe exposure does not end in death, marked central labular necrosis of the liver and cloudy swelling of the tubular epithelium of the kidneys is evident (3,8).

Orally, the acute toxic effects of ODCB are not of a high order. Guinea pigs fed 0.8 g/kg of body weight showed no toxic effects. However, large doses of 2.0 g/kg of body weight were fatal to all animals under study (8). If, however, the digestive tract is bypassed by injecting ODCB intravenously into the blood stream, it exhibits a higher order of acute toxicity. Administered in this fashion, doses of 330 mg/kg are lethal to rabbits, and 520 mg/kg will cause fatality in mice (7).

The effects of acute dermal exposure to ODCB in humans were reported in a German study cited by Hollingsworth (8). Pain in the form of a burning sensation, was evident in two human subjects 15 minutes after application of ODCB to the skin. The response became more intense during the total exposure time of one hour and subsided when the ODCB was washed off. Within 24 hours, the exposed area became red and a blister formed. As the blister healed, a brown pigment formed and did not disappear three months after exposure. Although acute dermal exposure to ODCB will cause this type of irritant action, the chemical is only slowly absorbed through the intact skin (4). Therefore, systemic intoxication by the skin route of exposure is insignificant.

The irritant properties of ODCB have also been demonstrated by Hollingsworth (8) on the eyes of rabbits. Introducing two drops of undiluted ODCB into the eyes of a rabbit caused immediate pain and slight conjunctival irritation. The condition, however, completely cleared in a period of 7 days.

In conclusion, the acute toxicity of ODCB is of a fairly low order. The good warning properties of the compound (odor; eye, skin, and respiratory irritation) at low concentrations (50-100 ppm), precludes extended human exposure to the extremely high concentrations of ODCB that would be required to produce effects of an acute nature (3,4,8).

V. Chronic Toxicity:

Available data on the chronic toxicity of ODCB is from Hollingsworth (8), and again shows the compound to exhibit a low order of toxicity. Chronic inhalation of ODCB vapors by a variety of animals were tested over a period of six to seven months with very little if any pathological damage. A group of rats, guinea pigs, and mice were exposed to concentrations of 49 ppm ODCB in air seven hours a day, five days a week without adverse effect. Similarly, rats, guinea pigs, rabbits, and monkeys were exposed in the same manner to average concentrations of 93 ppm ODCB in air for six to seven months, with only a slight decrease in the weight of the male guinea pig spleen noted. In addition to these experimental results, Hollingsworth (8) cites industrial hygiene surveys accumulated over a period of many years by the Dow Chemical Company, which indicate chronic inhalation of ODCB by workers causes no significant damage. Exposures in workroom air ranging from 1 to 44 ppm and averaging 15 ppm ODCB over extended periods showed no evidence of organic injury nor hematological effects in workmen.

Chronic oral exposure to ODCB has proven to be slightly more toxic than that of respiratory route of exposure, but this route of exposure has also failed to demonstrate a high order of toxicity. Concentrations of 376 mg/kg, 188 mg/kg, and 18.8 mg/kg ODCB were fed to rats via stomach tube, five days per week for a total of 138 doses in 192 days. Rats fed the highest concentration of 376 mg/kg showed no increase in mortality rate but did exhibit a weight increase of the liver and kidney and a weight decrease of the spleen. Microscopic examination of the liver revealed a slight to moderate cloudy swelling. Rats receiving 188 mg/kg also showed slight weight increases in the liver and kidneys, but without

the swelling noted at the highest concentration. Rats exposed orally to 18.8 mg/kg exhibited no observable adverse effects (8).

As stated earlier, if ODCB is absorbed at all through the skin, it is at an extremely slow rate, therefore, the danger of building toxic doses of ODCB in the body from chronic dermal exposure is negligible. However, it should be noted that doses applied to skin, that in themselves are too small to cause the irritant action associated of ODCB, may upon repeated exposure cause sensitization of the skin, leading eventually to dermatitis (8).

There is at the present time, some question about the ability of ODCB to be carcinogenic. Although never shown in laboratory experiments with animals, an association between leukemia and ODCB industrial exposures has been suggested. This evidence prompted the International Agency for Research on Cancer to evaluate the carcinogenic risk of ODCB in 1974. They concluded at that time that insufficient evidence existed to assess the carcinogenic potential of ODCB (5).

In summary, the chronic toxicity of ODCB is of a relatively low order. The route of exposure of most significance for chronic toxicity is the oral route, but even repeated ingestion of sizable quantities of ODCB causes only minimal effects.

VI. Environmental Toxicology:

The action of ODCB in the environment is not known. However, there is some evidence that suggests ODCB may show some degree of environmental persistence. ODCB is not known to occur in nature, therefore, any detectable quantities of the chemical in the environment can be directly linked to man's usage of ODCB (5). ODCB is an important

intermediate in the manufacture of the halogenated hydrocarbon pesticides. This class of pesticide, of which DDT, chlordane, and heptachlor are members, are noted for their persistence in the environment and their ability to biomagnify in the food chain. Although these insecticides are chemically more complex than ODCB, some consideration should be given to the possibility that ODCB, a simple halogenated hydrocarbon, may exhibit some degree of environmental persistence (3,5).

From the standpoint of industrial hygiene, the irritant action of ODCB on the eye, skin, and respiratory tract is of most concern. The Threshold Limit Value of 50 ppm which exists for ODCB was established as a ceiling value under which concentrations of this chemical should be held to deter its irritant properties. When used industrially, adequate ventilation is essential to prevent irritation of the respiratory tract from ODCB. Where skin contact is likely, protective clothing and impervious gloves should be worn and replaced at first sign of deterioration. Good personal hygiene practices should always be stressed. If an eye contact hazard exists, side-shield safety glasses should be worn (4). As previously indicated, ODCB possesses good warning properties which should prevent the acute overexposure of workers. However, the possibility of adaptation to these properties should be recognized (3). Chronic industrial exposure to ODCB, in most cases, will produce few adverse affects. However, liver and kidney damage may possibly result from long-term exposure, making periodic medical examinations for exposed workers a good practice. Pre-placement examinations should be used to channel workers with existing liver and kidney disease away from jobs that expose them to ODCB (3,4,8).

Perhaps the greatest danger of using ODCB in a solar heating and cooling system is connected with the flammability of the chemical. The flash point of ODCB is a relatively low 151⁰F. Since the proposed system will operate at internal temperatures around 200⁰F, the possibility of flammable concentrations of ODCB vapors being generated seems highly possible. If the possibility of combustion of ODCB vapors within the system exists or if the potential for vapor escape from the unit exists, the use of ODCB as a heat transfer medium is highly undesirable from a safety standpoint.

VII. Recommendation:

In view of the toxicological and safety information currently available, the use of ODCB as a heat exchange medium for solar heating and cooling is recommended with reservation. Although ODCB possesses a low order of toxicity in animal studies and limited human exposure data in industrial settings upholds these findings, its irritant properties, possible safety hazards, and unknown environmental degradation patterns make it less acceptable than some of the other chemicals previously under consideration. The use of a chemical that exhibits the low order of toxicity of ODCB, without possessing the irritant and safety properties in question, would be more desirable in a solar heating and cooling system that may find wide private and commercial use.

References

1. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. U.S. Govt. Printing Office. Washington, D.C. 1975.
2. Weast, R.C. Handbook of Chemistry and Physics. Chemical Rubber Company. Cleveland, Ohio. 1972.
3. Patty, F.A. Industrial Hygiene and Toxicology: Vol. II. Interscience Publishers. John Wiley and Sons, Inc. New York. 1967.
4. American Industrial Hygiene Association. Hygienic Guide Series: O-Dichlorobenzene. Southfield, Michigan. 1964.
5. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man: ortho and para-Dichlorobenzene. Volume 7. pp. 231-243. June, 1974.
6. Hamilton, A. and H.L. Hardy. Industrial Toxicology. Publishing Science Group, Inc. Acton, Massachusetts. 1974.
7. Cameron, G.R., et al. The Toxicity of Certain Chlorine Derivatives of Benzene With Special Reference to O-Dichlorobenzene. Journal of Pathology and Bacteriology. Vol. 44, No. 2. pp. 281-296. 1937.
8. Hollingsworth, R.L., et al. Toxicity of o-Dichlorobenzene. A.M.A. Archives of Industrial Health. Vol. 17. pp. 180-187. March, 1958.
9. American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values. Third Edition. Cincinnati, Ohio. 1974.

TOXICOLOGICAL EVALUATION OF ORTHO-PHENETIDINE

August 4, 1976

ABSTRACT

Ortho-phenetidine is one of a group of aromatic amines noted in general for their methemoglobin forming properties. There is only limited and conflicting data available concerning the toxicity of this chemical. At present there are no hygienic standards for ortho-phenetidine and nothing is known about its environmental toxicology. Because of the absence of literature and due to its probable methemoglobin forming properties, ortho-phenetidine is not recommended for use in solar energy heating or cooling units.

I. Chemical Properties:

Name: Ortho-phenetidine

Molecular formula: $\text{NH}_2\text{C}_6\text{H}_4\text{OC}_2\text{H}_5$ or $\text{C}_8\text{H}_{11}\text{NO}$

Molecular weight (1): 137.18

Synonyms (1): 2-aminophenetole; 2-ethoxyaniline; o-aminophenol ethyl ether.

Melting point: -4°F

Boiling point: 442°F

Specific gravity: 1.065

Refractive index (1): $N_D = 1.5560$ @ 20°C

Solubility (1): water - slightly soluble; alcohol - soluble; ether - soluble.

Vapor pressure (2): 1 mm @ 67°C

Appearance (2): oily liquid

II. Hygienic Standards:

There are presently no available standards for O-phenetidine.

III. General Toxicity:

Ortho-phenetidine is one of a group of chemicals known as the aromatic amines. In general, these chemicals are similar not only in their chemical properties but in their toxicology as well (3). The aromatic amines

are used in a variety of industries such as in the production of dyes, rubber and rubber antioxidants, in the operation and production of drugs, cosmetics and foods and in the dyeing industry (4). Most of these compounds have the ability to form methemoglobins in man which causes tissue hypoxia and cyanosis (3,5). Many of the aromatic amines are recognized as, or are suspected of being carcinogens. The primary routes of exposure are absorption through the skin or the respiratory tract (3,4,5,6).

IV. Acute and Chronic Toxicity:

There is no data available on the acute or chronic toxicity of ortho-phenetidine. A related compound, p-phenetidine, has been shown to cause methemoglobin in dogs (8). In a Japanese abstract on the antipyretic action of alkyl ether compounds of p- and o-amino phenols the lethal dose for o-phenetidine in mice was found to be 0.6 g/kg (9). The method of administration of the chemical was not mentioned. In a study involving chemicals in foods, o-phenetidine was claimed to be 1,400 times as sweet as sucrose. Its safety was questioned, however, because of the toxicity of its normal propyl homologue.

V. Human Toxicity:

There is no available information on the toxicity of o-phenetidine to humans. Because of its relatively low solubility in water and high solubility in organic solvents this chemical has the potential to readily penetrate the skin (3). Sax (2) states that this chemical is a recognized carcinogen although there is no supporting data available upholding this statement. Clayson (6) states that for an aromatic amine to be potentially active as a carcinogen the amino group must be attached to more than one aromatic ring and the attachment para to the amino group must be filled by

another substituent or by part of the conjugated system. Recent studies have found, however, that even simple structures with only one ring and substituents at a position other than para are carcinogenic (7). Ortho-phenetidine, with only one aromatic ring and an ortho-substituent, has, therefore, the potential of being a carcinogen although this has yet to be tested. This chemical is probably a methemoglobin former as evidenced by its isomer p-phenetidine, although there is no specific data documenting this probable characteristic (8).

VI. Environmental Toxicology:

There is no available literature on the effects of o-phenetidine on the environment. It is only slightly water soluble, therefore aquatic transport is unlikely (1). When heated to decomposition, this chemical will form highly noxious gases of nitrogen oxides (2).

VII. Recommendations:

Ortho-phenetidine is one of a group of aromatic amines known in general for their methemoglobin forming properties. The one acute toxicity abstract available suggests that this chemical is slightly toxic when administered in an unknown manner to mice. Another source states that ortho-phenetidine is a recognized carcinogen but there is no substantiating evidence of this. In view of the conflicting and limited toxicity data available, and considering the toxic nature of its chemical relatives, ortho-phenetidine is not toxicologically recommended for use in solar energy heating or cooling units.

References

1. Weast, R. 1972. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Co. Cleveland, Ohio.
2. Sax, Irving H. 1975. Dangerous Properties of Industrial Materials. Van-Nostrand - Reinhold Company.
3. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers, John Wiley and Sons, Inc. New York.
4. Hueper, W.C. and W.D. Conway. 1964. Chemical Carcinogenesis and Cancers. Charles C. Thomas. Springfield, Illinois.
5. Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology. Publishing Science Group, Inc. Acton, Massachusetts.
6. Clayson, David. 1962. Chemical Carcinogenesis. Little, Brown and Company. Boston, Massachusetts.
7. Casarett, Louis and John Doull. 1975. Toxicology. Macmillan Publishing Company. New York.
8. Chemical Abstracts. #891h, Vol. 56. Baader, Helmut, et al. Effects of age on transformations of phenacetin, p-phenetidine, N-acetyl-p-amino phenol, p-amino phenol, and aniline in the dog. Arch. Exptl. Path. Pharmacol. (German).
9. Chemical Abstracts. #132081, Vol. 51. Ishibashi, Tetsuro. Anti-pyretic actions of alkyl ether compounds of pando-aminophenols. Nippon Yakurigaku (Japanese).
10. Chemical Abstracts. #2703e, Vol. 46. Lehman. Chemicals in Foods: A Report to the Association of Food and Drug Officials on Current Developments. Assoc. Food and Drug Off. U.S. Quart. Bull.

TOXICOLOGICAL EVALUATION OF DIVINYL BENZENE

September 3, 1976

ABSTRACT

Divinyl benzene is one of several chemical compounds in the large chemical family known as the aromatic hydrocarbons. More specifically, divinyl benzene is a di-alkyl derivative of benzene, commonly referred to as simply an alkylated benzene. Although the alkylated benzenes are among the most important of industrial chemicals, divinyl benzene seems to be only sparsely used. Consequently, toxicological information about the chemical is extremely limited. In general, the alkylbenzenes are classified as moderately toxic compounds, possessing the ability to cause central nervous system depression and primary irritation of the respiratory tract, eyes, and skin. The most toxic of the alkylbenzenes are noted for their ability to induce a pneumonitis of the lungs and a dermatitis of the skin. The alkylbenzenes do not, however, attack the blood forming tissues like their parent compound, benzene. The relative toxicity of the alkylbenzenes is dependent upon chemical structure, and it would appear that the structure of divinyl benzene would considerably minimize its toxic potential. It must be pointed out, however, that little experimental data exists to uphold this speculation. Finally, the safety of divinyl benzene as a heat exchange medium is questioned because its flash point is below the expected operating temperatures of the proposed solar system, giving rise to the possibility of a potential fire hazard.

On the basis of toxicological and safety information currently available, divinyl benzene is recommended for use as a heat exchange medium for solar heating and cooling only with reservation. Chemicals that have been proven toxicologically safe from indepth research should be given preference over divinyl benzene if at all possible.

I. Chemical Properties:

Name: divinyl benzene

Molecular formula: $C_6H_4(CH:CH_2)_2$

Molecular weight (1): 130.20

Synonyms (1): DVB, vinyl styrene, m-divinylbenzen (Czech)

Freezing point: -88°F

Boiling point: 383°F

Flash point: 165°F

Specific gravity: 0.9289

Viscosity: 1.09 centipoises @ 68°F

II. Hygienic Standards:

There are presently no available standards for exposure to divinyl benzene.

III. Toxicology:

Divinyl benzene is one of many chemical compounds that belong to the large chemical family known as the aromatic hydrocarbons. More specifically, divinyl benzene is one of the di-alkyl derivatives of benzene and is commonly known as alkylated benzene. Benzene and its alkyl derivatives are obtained as by-products of the coke oven industry and the petroleum industry (2). They are some of the most important industrial chemicals in use today. Recognized mainly for their excellent solvent properties in

the chemical and drug industries, benzene and its alkyl derivatives are also the starting materials and intermediates in the synthesis of numerous chemicals, and are used as constituents of aviation and automotive fuels (2). Although the alkylated benzenes are among the most important of industrial chemicals, it appears that divinyl benzene does not share in their importance. Extremely little information is available that details the industrial usage patterns of this chemical. Consequently, essentially no data has been generated with which to assess the toxicology of divinyl benzene. However, some generalizations can be made from what is known about the toxicology of benzene and the alkyl benzenes as a group.

In general, the liquid alkylated benzenes can be classified as central nervous system depressants and primary irritants (3). Although few LD_{50} and no LC_{50} values exist for divinyl benzene, those established for other alkyl benzene derivatives indicate that they are moderately toxic by inhalation and moderately to slightly toxic by oral and dermal routes of acute exposure. The two LD_{50} values found for divinyl benzene seem to uphold this generalization. Gerarde (3) lists an oral LD_{50} for rats as 5 ml/kg, and a Russian study cited by the Registry of Toxic Effects of Chemical Substances also gives an oral LD_{50} for rats of 4.04 g/kg. Both of these values indicate that divinyl benzene is only slightly toxic from acute oral exposure.

Although acute oral exposure is of concern because of the ability of alkylated benzenes to irritate the gastrointestinal tract, more attention has been given to the respiratory and dermal routes of exposure. Inhalation of alkylbenzene vapors leads to two physiological responses. The first is central nervous system depression. Alkylbenzenes have a particular affinity for nervous tissues because of the high lipid content in these

tissues. Once concentrated in sufficient amounts, the alkylbenzenes cause a syndrome characterized by sluggishness, stupor, anesthesia, blurred vision, narcosis, and coma (3,4). With large enough doses, permanent damage may occur, especially to the brain. The second effect of inhalation of alkylated benzene vapor is severe irritation of the mucous membranes and pulmonary tissue. Contact of the vapor with mucous membranes causes local irritation and vasodilation that will subside rather quickly when exposure ceases. However, aspiration of small volumes of alkylbenzene into the lungs can cause severe damage. Because of their low surface tension, alkylbenzenes spread over large areas of the lung causing a pneumonitis characterized by pulmonary edema, hemorrhage, and tissue necrosis. Damage can be permanent and death may occur from respiratory paralysis (3).

The irritant potential of the alkylated benzenes is also exhibited upon contact of the chemicals with the eyes and skin. Ocular exposure to alkylbenzenes causes itching, lacrimation, and irritation that can result in tissue injury with prolonged exposure (3). Dermal acute exposure to alkylated benzenes produces vasodilation, erythema, and irritation of short duration. Long term exposure results in a dermatitis caused by removal of natural cutaneous fats that leave the skin dried, scaled, and fissured (3). However, alkylbenzenes are only slowly absorbed through the skin, making systemic intoxication improbable from dermal exposure.

The effects of chronic exposure to alkylated benzenes are generally the same as those from acute exposure; central nervous system depression and primary irritation of the respiratory tract, eyes, and skin. Although alkylbenzenes have been suspected of attacking blood-forming tissues like their parent compound, benzene, extensive animal experimentation indicates that they possess no myelotoxic potential. For this reason, it has been proposed that the alkylbenzenes be referred to as "phenylalkanes" to

disassociate them from the more toxic benzene (2).

From the generalized toxicology of the alkylbenzenes it might be suspected that divinyl benzene is a rather toxic chemical. However, the toxic potential of the alkylated benzenes is closely tied to chemical structure. The relative toxicity of an alkylated benzene depends on its water solubility, the number of alkyl groups on the benzene ring, and the length of the side chains (3). The toxic potential of the alkylbenzenes decreases as water solubility decreases, number of alkyl groups increases, and length of the side chain decreases. Since divinyl benzene is a short chain, disubstituted, water insoluble compound, it is reasonable to suspect that its toxic potential might be much less than that of other alkylated benzenes.

The environmental and industrial toxicologies of divinyl benzene are not known. However, since alkylated benzenes are petroleum by-products, they may exhibit some of the potential of other petroleum products to be environmentally persistent and, therefore, should be treated with care. In the industrial environment, the toxicity that the alkylbenzenes exhibit can be minimized by sound industrial hygiene practices. Adequate ventilation of work areas is essential, and chemical cartridge respirators and impregnable gloves should be worn when exposure is suspected.

In conclusion, it should be noted that divinyl benzene may not be acceptable for use as a heat transfer agent from a safety standpoint. It's flash point of 165°F is below the expected internal operation temperature of the proposed system, giving rise to the possibility of flammable concentrations of divinyl benzene vapors being generated. If combustion of these vapors within the system could occur, or if the vapors could potentially escape from the unit, the use of divinyl benzene as a heat transfer medium is undesirable from a safety standpoint.

IV. Recommendations:

In view of toxicological information currently available, divinyl benzene is recommended for use as a heat exchange medium for solar heating and cooling only with reservation. Although none of the alkylbenzenes exhibit an extremely toxic potential, if handled improperly they can cause significant human injury. However, the relative toxicity of the alkylbenzenes is dependent upon their chemical structure and it would appear the divinyl benzene possesses a structure that would tend to considerably minimize its toxic potential. It should be pointed out, however, that essentially no experimental data exists to uphold this speculation. In addition, there is some question about the safety of using divinyl benzene as a heat transfer medium because of its low flash point. For these reasons, preference should be given to chemicals that have been proven toxicologically safe from indepth research.

References

1. National Institute of Occupational Safety & Health. Registry of Toxic Effects of Chemical Substances, Rockville, Maryland. 1975.
2. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers. John Wiley and Sons, Inc. New York. 1967.
3. Gerarde, H.W. Toxicology and Biochemistry of Aromatic Hydrocarbons. Elsevier Publishing Company. Amsterdam. 1960.
4. Deichmann, W.B. and H.W. Gerarde. Toxicology of Drugs and Chemicals. Academic Press, Inc. New York. 1969.

TOXICOLOGICAL EVALUATION OF META-CHLOROANILINE

September 7, 1976

ABSTRACT

Meta-chloroaniline is one of a group of aromatic amines noted in general for their methemoglobin forming properties. The available acute and chronic toxicity data indicates that liver and kidney damage as well as methemoglobinemia may be induced by any of the exposure routes. Hygienic standards for air concentrations of m-chloroaniline have been proposed in Russia (0.05 mg/m^3), however, the United States has no standards available at this time. The aquatic toxicity of this chemical has been shown to be slight.

Based on the toxicological information available, meta-chloroaniline is not recommended for use in solar energy heating or cooling units.

I. Chemical Properties:

Name: Meta-Chloroaniline (m-chloroaniline)

Molecular formula: $\text{Cl C}_6\text{H}_4\text{NH}_2$ or $\text{C}_6\text{H}_6\text{Cl N}$

Molecular weight (1): 127.52

Synonyms (1): 3-chlorobenzenamine; 1-amino-3-chlorobenzene;
meta-chlorobenzene; 3-chlooranilinen (Dutch); 3-chloroaniline;
3-chlorophenylamine; 3-chloroaniline (Italian); fast orange GC
base; orange GC base.

Boiling point: 443°F

Melting point (2): -10.4°C

Freezing point: 14°F

Specific gravity: 1.223

Refractive index (3): $n_D = 1.59414$

Solubility (3): water - insoluble; alcohol, ether, acetone, benzene, CCl_4 - miscible; organic solvents - soluble.

Appearance (2): liquid

Odor (2): characteristic sweet odor

II. Hygienic Standards:

There are presently no United States standards for m-chloroaniline.

Russia recommends a maximum allowable air concentration of 0.05 mg/m³.

III. General Toxicity:

Meta-chloroaniline is one of a group of chemicals known as the

aromatic amines. In general, the chemicals of this series are characterized by the substitution of a hydrogen on the benzene ring for an amino radical to form aniline (2). Other radicals may then be added to form a variety of aniline homologs. The aromatic amines are used in a variety of industries such as in the production of dyes, rubber and rubber antioxidants, in the operation and production of drugs, paints, varnishes, shoe polishes, cosmetics, pesticides, plastics, petroleum products and synthetic resins. Specifically, m-chloroaniline is used in the synthesis of dye stuffs, insecticides and as an intermediate for other industrially important chemicals (2,4,5).

In general, the aromatic amines are similar not only in their chemical properties but in their toxicology as well (2). While many aromatic amines are known carcinogens or suspected of being carcinogenic, the term "aniline tumor" of the bladder is erroneous in that aniline or its immediate homologs have never clearly been demonstrated to be carcinogens (2,6). The major toxicological characteristic of these compounds is their ability to form methemoglobin in humans which induces tissue hypoxia and cyanosis (2,6). The primary routes of exposure are absorption through the skin or the respiratory tract, therefore, the volatility of the chemical and its ability to penetrate the protective fat components of the skin will determine the relative toxicity of the chemical in question (2,6).

IV. Acute Toxicity:

All of the available toxicological studies involving m-chloroaniline originated in Russia.

When administered orally, this chemical appears to be of a moderate toxicity in test animals, however, the symptoms included cyanosis which

demonstrated m-chloroaniline's ability to cause methemoglobinemia (4). Other symptoms observed were muscular weakness, muscle spasms, slow respiration and loss of orientation and the ability to react to pain. Table I shows the results of various acute oral toxicity studies.

Table I.
Acute oral toxicity values for m-chloroaniline.

<u>Animal</u>	<u>LD₅₀ (mg/kg)</u>	<u>Reference</u>
Mice	228	7
Mice	1100	4
Rats (female)	1034	4
Rats (male)	880	4
Guinea pigs	750	4

A German study, as reported by the Registry of Toxic Effects of Chemical Substances (1), on the subcutaneous injection of m-chloroaniline in cats resulted in a lethal dose of 310 mg/kg.

Dermal studies have shown that this chemical may be readily absorbed through the skin. The application of this chemical to intact cat skin has resulted in LD₅₀'s of 223 mg/kg and 239 mg/kg with the occurrence of dermatitis and scarring (7,8). An LD₅₀ of 334 mg/kg was reported for the application of m-chloroaniline to the stomach of mice (8).

Although inhalation is not a likely exposure route, due to the high boiling point of m-chloroaniline, it should be noted that exposure to the vapors of this chemical may result in methemoglobinemia.

V. Chronic Toxicity:

Very little data is available on the chronic toxicity of m-chloroaniline.

The literature that is available comes from Russian environmental studies. Chronic oral exposure to m-chloroaniline was studied by administration over a 3-month period of doses equivalent to 1/10 the LD₅₀ for rats, i.e. 110 mg/kg (4). The results were cyanosis, a decrease in mobility and a rise in inhibition. Metabolic tests showed changes in liver and kidney functions. A rise in the blood of methemoglobin and in the urine of urobilin was also observed.

A chronic dermal study by Kondrashov (8) involved the application of 20 percent of the acute LD₅₀ to the stomach of mice for 5 weeks. This dose level of approximately 66.8 mg/kg resulted in effects similar to those exhibited by aniline after the examination of body and organ weights, the number of erythrocytes and the amount of hemoglobin and methemoglobin in the blood. Aniline is known to cause methemoglobinemia in man (3).

VI. Human Toxicity:

There is no available data concerning the effect of m-chloroaniline on humans. The available animal studies, both acute and chronic, indicate that this chemical may have the ability to cause methemoglobinemia in humans and possibly liver and kidney damage (4,5,7,8). Although no hygienic standards have been set for this chemical in the United States, Russian scientists have proposed a maximum permissible concentration of m-chloroaniline in the air of 0.05 mg/m³ based on the concentration of 1.5 mg/m³ which was found to cause chronic intoxication in rats (9).

VII. Environmental Toxicology:

On the basis of toxicity to aquatic life, m-chloroaniline was found to be slightly toxic (1). Aquatic organisms were tested at various concentrations of m-chloroaniline until it was determined that a concentration

of 10 mg/l to 100 mg/l would kill 50 percent of the test organisms within 96 hours. A Russian study to determine a maximum permissible concentration of m-chloroaniline in water storage reservoirs recommended a concentration of 0.2 mg/l based on the toxicity of the compound (4). This same study determined the threshold for detection by odor of m-chloroaniline as being 3 mg/l.

In an occupational setting, various hygienic procedures should be incorporated when using any of the aromatic amines. Primarily, these procedures involve the avoidance of contact with any of these chemicals through competent engineering of the workplace, proper medical supervision and, in general, maintenance of sound industrial hygiene practices.

VIII. Recommendations:

Meta-chloroaniline is a moderate methemoglobin former and as such would be a potentially dangerous chemical to use in solar energy units. Additionally, this chemical has the ability to cause liver and kidney damage. Meta-chloroaniline is not recommended for use in solar energy units with respect to the toxicology of the chemical.

References

1. National Institute for Occupational Safety and Health. 1975. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland.
2. Patty, Frank. 1963. Industrial Hygiene and Toxicology. Vol. II. Interscience Publishers. John Wiley and Sons, Inc. New York.
3. Weast, R. 1971. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio.
4. Khamuev, G.D. 1967. The Maximum Permissible Concentration of p-Chloroaniline and m-Chloroaniline in Water Bodies. Hygiene and Sanitation (English translation of Gigenia i Sanitariya) (Russia), 32: 15.
5. Chemical Abstracts. #1236f. Vol. 66. Khamuev, G.D. Chlorinated Anilines and Their Sanitary-Toxicological Characteristics. Khim. Faktory Vneshn. Sredy i ky. Gigen. Znachenie, Sb., Moscow.
6. Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology. Publishing Science Group, Inc. Acton, Massachusetts.
7. Chemical Abstracts. #68958q. Vol. 71. Kondrashov, V.A. Toxic Action of Chloroaniline and Aniline Fumes through the Intact Skin. Gig. Tr. Prof. Zabol. (Russia).
8. Chemical Abstracts. #64483f. Vol. 73. Kondrashov, V.A. Toxicology of Chloroanilines and Aniline. Tr., Gos. Inst. Prikl. Khim. (Russia).
9. Chemical Abstract. #129098f. Vol. 73. Fvedai, V.I. Toxicology of Isomeric p- and m-chloroanilines and Experimental Justification of the Maximum Permissible Concentration of these Substances in the Air of Working Places. Farmakol. Toksikol. 19 (Russia).

TOXICOLOGICAL EVALUATION OF ORTHO NITROTOLUENE

September 9, 1976

ABSTRACT

Ortho nitrotoluene (ONT) is a member of a chemical family known as the aromatic nitro compounds. A member of an industrially important chemical family, ONT is used in the synthesis of dyestuffs, explosives, and a number of important chemical intermediates. As a group, the aromatic nitro compounds are toxicologically recognized for their ability to produce methemoglobin in man. This physiological syndrome, known as methemoglobinemia, prevents oxygen in the blood from being available to body tissue causing a cyanosis that can be severe. In addition, the aromatic nitro compounds may be potent skin sensitizers and are often capable of causing liver damage from which recovery is rare. Although ONT is generally not considered to be as toxic as many of its chemical relatives, it is capable of causing the formation of methemoglobin at relatively low concentrations. Information implicating ONT as a skin sensitizer or a hepatotoxic agent could not be found, but these possibilities should not be ruled out. The action of ONT in the environment is generally unknown and in the industrial setting exposure to ONT can be controlled only with sound industrial hygiene practice.

In view of the toxicological information currently available, ortho nitrotoluene is not recommended for use as a heat exchange medium for solar heating and cooling.

I. Chemical Properties:

Name: ortho nitrotoluene

Molecular formula: $C_7H_7NO_2$

Molecular weight (1): 137.14

Synonyms (2): ortho-methylnitrobenzene; 2- methylnitrobenzene;

1 - methyl - 2 - nitrobenzene; Toluene, o-nitro; ONT

Freezing point: 25°F

Boiling point (1): 429°F, 220.4°C

Flash point: 223°F

Specific gravity: 1.1629

Refractive index: $n_D = 1.5450$ @ 20°C

Percent in saturated air: 0.21 @ 60°C

Solubility (1,3): insoluble in water (0.0652 @ 30°C); infinite in
alcohol, ether, benzene, and chloroform

Physical state (4): yellow liquid

II. Hygienic Standards:

TLV: Air 5 ppm (approximately 30 mg/m³)

(OSHA Standard 1910.93) and (ACGIH 1971)

This chemical may be absorbed through the skin.

III. Toxicology:

Ortho-nitrotoluene (ONT) is a member of the chemical family known as the aromatic nitro compounds. As a group, these compounds have great industrial importance as intermediates in the synthesis of a variety of commercial products. More specifically, ONT is a mono-nitro derivative of toluene, formed by the nitration of toluene in the presence of sulfuric and nitric acids (4). ONT is most widely used in the synthesis of dyestuffs and explosives, as well as other industrially important intermediates (3).

As a group, the aromatic nitro compounds have been studied extensively. For the most part, they are similar in chemical properties, as well as in pharmacological or toxicological effects. The most common outstanding toxicological property of the aromatic nitro compounds is their ability to form methemoglobin in man. Methemoglobin is the oxidation product of natural hemoglobin in the blood and may be considered a true oxide, in which one atom of oxygen combines with one atom of iron (3). In other words, methemoglobin is formed when the iron of the heme radical is oxidized from the ferrous to the ferric state. When this occurs, oxygen bound to the methemoglobin is so firmly attached that it is not available to tissues, resulting in a hypoxia that can be severe. In addition, methemoglobin also interferes with the release of oxygen from normal hemoglobin so that the hypoxia is more severe than the methemoglobin levels might suggest (5).

When methemoglobin is produced by the action of the aromatic nitro compounds, a syndrome known as methemoglobinemia is produced, characterized by a distinct cyanosis. The cyanosis is first noted at the lips and ears, where the blue appearance of the skin indicates the lack of sufficient oxygen (6). Cyanosis may become apparent with concentrations of methemoglobin approximating 15 percent, and although blue tint of the skin may be the

only symptom until methemoglobin levels reach 40 percent, euphoria and headache are common (3,5). At higher levels, headache may become severe accompanied by weakness, ataxia, and lightheadedness. In addition to the effects that the aromatic nitro compounds have on the blood, they also exhibit a toxic action on nervous tissue. Severe poisonings may be accompanied by tremors or convulsions, arrest of respiration, or total collapse (3,6).

Methemoglobinemia is an acute reaction to exposure to aromatic nitro compounds. As a general rule, the rate of appearance of methemoglobinemia is dependent upon the nature, duration, and intensity of exposure (3). The routes of exposure with most significance are the respiratory and dermal routes. Vapors of the aromatic nitro compounds are quickly absorbed by the lungs, and most of the compounds are readily passed through intact skin (3,5,6,7). Even though methemoglobinemia may develop alarmingly fast and be quite severe, methemoglobin is reduced to normal hemoglobin rather quickly with no apparent permanent damage. Treatment of a poisoned individual normally consists of no more than a thorough washing of all parts of the body and flushing of the nasal cavity to remove all traces of the aromatic nitro compound followed by bed rest. In most cases, methemoglobinemia is completely reversed within 24 hours (3).

The chronic effects of exposure to aromatic nitro compounds are not as well defined as the acute effects. However, almost all of the compounds are powerful skin sensitizers and some of the chemicals have shown a toxic potential for the liver (3,5). Hepatotoxic effects are often associated with an aplastic anemia manifested by jaundice. Unfortunately, the jaundice does not appear as a warning signal until the late stages of the disease, and recovery from liver injury induced by aromatic nitro compounds is rare (3,5).

Although much is known about the toxicology of the aromatic nitro compound group, the specific toxicity of ONT is obscure. Little research appears in the literature and that which is available conflicts. Early research indicates that ONT is as toxic as nitrobenzene, a strong methemoglobin former capable of producing hepatotoxic effects (4). More recent work compares ONT to aniline, a less toxic compound that still possesses the ability to cause methemoglobinemia, but only at higher levels of exposure (6,7). This comparison would seem the more valid of the two since ONT is usually considered a methemoglobin former of low grade because cases of ONT poisoning are not very common (3,4,7). Nevertheless, ONT has been assigned a rather low TLV of 5 ppm by ACGIH to protect workers from the chemical's methemoglobin forming powers (7). The potential of ONT to be chronically toxic is questionable. Although its chemical relatives are known skin sensitizers and hepatotoxic agents, none of the information currently available implicates ONT to have either of these potentials despite the fact that it is readily absorbed by intact skin.

The toxic potential of ONT in the environment is also vague. Data assessing the biodegradability and food chain transport mechanisms of this compound is not currently available. However, an aquatic toxicity has been assigned to ONT by the 1975 Registry of Toxic Effects of Chemical Substances. A TL_m 96 value ranging from 10 ppm to 100 ppm is given to the chemical. This is the concentration range of ONT which will kill 50 percent of exposed aquatic test organisms in 96 hours, and can be interpreted to mean that ONT is only slightly toxic to aquatic life (2).

In the industrial environment, exposure to ONT can and has been effectively controlled as evidenced by few reports of ONT poisoning. Keeping the ambient air concentration of ONT below the suggested TLV and

preventing dermal contact with the chemical has minimized the number of acute ONT poisonings. This has been accomplished by providing adequate ventilation at the source of exposure, use of impregnable gloves, daily laundering of work clothes, mandatory showers at the end of each work shift, and constant medical surveillance of exposed personnel (3).

IV. Recommendations:

On the basis of toxicological information currently available, ortho nitrotoluene is not recommended for use as a heat exchange medium for solar heating and cooling. Although ONT is generally believed to be less toxic than some of its chemical relatives, it still can cause methemoglobinemia at relatively low concentrations. In addition, the possibility that ONT may be a skin sensitizer or possess hepatotoxic potential should not be ruled out until sufficient research is available to confirm its lack of these toxic abilities. In a controlled environment, similar to that in an industrial setting, ONT can be adequately controlled to minimize the danger of poisoning. However, if the proposed solar system finds widespread public use, the controlled environment is lost and accidental intoxication by ONT becomes possible. For these reasons, use of a chemical that has been proven toxicologically safe through extensive research should be shown preference over ONT.

References

1. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
2. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
3. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
4. Von Oettingen, W.F. The Aromatic Amino and Nitro Compounds, Their Toxicity and Potential Dangers. U.S. Public Health Service. Public Health Bulletin. No. 271. 1941.
5. Hamilton, A. and Hardy, H.L. Industrial Toxicology. Publishing Science Group, Inc. Acton, Massachusetts. 1974.
6. National Safety Council. Fundamentals of Industrial Hygiene. Chicago, Illinois. 1975.
7. American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values. Third edition. Cincinnati, Ohio. 1974.

TOXICOLOGICAL EVALUATION OF CREOSOTE COAL TAR

July 22, 1976

ABSTRACT

Creosote Coal Tar is a chemical conglomerate resulting from the distillation of coal tar, that has numerous uses as a therapeutic agent and as an industrial chemical. Information currently available indicates that the toxic potential of the chemical is great. Although its acute toxicity is generally considered moderate, it is readily absorbed by the skin and the intestinal tract. Acute exposure to creosote can cause eye damage as well as irritation of the skin, mucous membranes and intestinal tract. The chronic toxicology of creosote is an area of great concern. Chronic dermal exposure to creosote causes a marked photodermatitis. In addition, and of greatest concern, creosote is a recognized carcinogen of the skin and a suspected carcinogen of the lung. In the environment, creosote seems to be rather persistent as well as moderately toxic to aquatic life. The toxic potentials of creosote carry over into the industrial setting, but can generally be controlled with good industrial hygiene practices. Finally, the safety of creosote as a heat exchange medium is questioned because its flash point is well below the expected operating temperatures of the proposed solar system, making the possibility of fire hazard great.

In view of the toxicological and safety information currently available, the use of Creosote Coal Tar as a heat exchange medium for solar heating and cooling is not recommended.

I. Chemical Properties:

Name: Creosote Coal Tar

Molecular Formula: Creosote distilled from coal tar contains guaiacol, creosol, phenol, pyrol, pyridene, and other aromatic compounds (1).

Molecular Weight: Varies with purity (1)

Synonyms: Brick Oil, Coal Tar Oil, Creosote Oil, Heavy Oil, Liquid Pitch Oil, Naphthalene Oil, Tar Oil, Wash Oil (2)

Boiling Point: 400°F

Flash Point: Closed Cup: 73.9°C (165°F)
Open Cup : 85°C (185°F) (1)

Auto-ignition Point: 637°F (3)

Specific Gravity: 1.07

Solubility: Slightly soluble in water; miscible with alcohol, ether, fixed or volatile oils; soluble in glycerin and solutions of fixed alkali hydroxides (1)

Physical State: Yellowish to colorless, flammable, oily liquid (may be a brown color because of impurities or oxidation) (1)

II. Hygienic Standards:

There are presently no available standards for exposure to creosote coal tar.

III. General Toxicology:

Creosote Coal Tar is a chemical conglomerate obtained by the distillation of coal tar at temperatures of 200 to 250°C (1). This crude form of creosote can be purified by further distillation and extraction

from suitable oils until the final preparation consists mainly of guaiacol and creosol, with numerous other aromatic compounds present in small amounts.

Creosote has had numerous applications through the years, both as a medicinal agent and as an industrial chemical. Medicinally, it has been used as an antiseptic, disinfectant, antipyretic, astringent, styptic, germicide, and as a therapeutic agent. Industrially, creosote serves as a lubricant for die molds, as an agent for waterproofing, as a wood preservative, as a constituent of fuel oils, and in the manufacture of chemicals (1).

Because of its diverse chemical makeup, creosote does not belong to a distinct chemical family. Although Patty (1) classifies it as a phenolic compound since many of its constituent parts are derivatives of phenols, creosote does not really resemble any other phenolic compound chemically or toxicologically. Therefore, it is impossible to summarize the toxicity of the phenolic group of chemical compounds as it applies to creosote. As it stands alone, creosote acts toxicologically as a systemic poison when orally ingested, capable of causing injury to the eye, dermatitis of the skin, and cancer upon chronic exposure (1,4,5).

IV. Acute Toxicity:

In light of the extreme toxicity that creosote exhibits from chronic exposure, the acute toxicity of this chemical seems rather insignificant. However, some acute toxicity data for creosote does exist for oral and dermal routes of exposure.

When ingested orally, creosote acts as a severe systemic poison that can be lethal upon intake of sufficient quantities. Table I summarizes the LD₅₀ values for animals obtained from acute oral exposure to

creosote. In general, signs of animal intoxication are the same as those for humans.

TABLE I.
Acute Oral LD₅₀ Values for Creosote Coal Tar.

<u>Animal</u>	<u>LD₅₀ (g/kg)</u>	<u>Reference</u>
Pigeon	0.1	1
Rabbit	0.6 - 0.8	1
Cat	0.6 - 0.8	1
Dog	0.6 - 0.8	1
Rat	0.725	

However, in the rat central nervous system depression was marked and comatose reactions were noted before death (6). The LD₅₀ values indicate that the acute oral toxicity of creosote in animals is only slight, but cattle have been fatally poisoned by licking creosote from treated telephone poles (1). Microscopic examination of fatally poisoned animals shows intense irritation and congestion of the entire gastrointestinal tract. In humans, fatalities have occurred 14 to 36 hours after ingestion of creosote in amounts of 7 grams for adults and 1 to 2 grams for children. The human symptomology of systemic illness closely parallels that in animals and includes salivation, vomiting, respiratory difficulties, thready pulse, vertigo, headache, loss of pupillary reflexes, hypothermia, cyanosis, and mild convulsions (1).

Direct contact of creosote with the eyes, mucous membranes, or skin can also cause an acute toxic reaction. The most common toxic effect

of creosote on the eyes is keratitis. Creosote splashed in the eyes in small quantities will cause discomfort but not great pain, followed by a blurring of vision. At this point, hazy superficial keratitis can be seen and vision usually remains permanently impaired (7). Creosote can also cause conjunctivitis and abrasion of the cornea with permanent corneal scars resulting in one-third of all cases of creosote contacting the eye (1). When applied directly to mucous membranes or skin, creosote may induce an intense burning and itching with local erythema. However, dermal contact with this compound is much more injurious from chronic exposure because of its phototoxic and carcinogenic potentials (1).

In conclusion, although creosote possesses lethal potential from acute exposure, its acute toxicity is generally considered to be moderate. When large doses of the chemical are fatal, death is caused by cardiovascular collapse. Creosote is readily absorbed through the intestinal tract and intact skin and is excreted from the body largely in the urine and to some extent by the lungs (1).

V. Chronic Toxicity:

By far, creosote's greatest toxic action is realized from chronic dermal exposure. However, there have been reports of chronic intoxication in humans from long-term oral exposure. Repeated absorption of therapeutic doses of creosote by the gastrointestinal tract can cause illness characterized by disturbance of vision and digestion, increased peristalsis, and excretion of bloody feces. In isolated cases, creosote has been suspected of causing hypertension and even general cardiovascular collapse (1).

The toxic action of creosote on the skin from chronic exposure has solicited much concern and research since early in the chemical's history. As previously stated, creosote is readily absorbed through intact skin, but in addition to this phenomenon, it can be the cause of severe skin disorders because of its phototoxic and carcinogenic capabilities. Creosote, like coal tar and all other volatile derivatives of the tar, can produce a severe phototoxic contact dermatitis in a large percent of the population. Unlike many other forms of dermatitis that are caused by immune mechanisms, a phototoxic dermatitis depends on the interaction of light and the photosensitizing chemical (4). Each phototoxic compound is activated by a specific wavelength of light that is dictated by chemical structure. For creosote, that wavelength is between 3,500 and 4,000 angstroms. When light in this range and creosote interact, the result is a photodermatitis that appears as a severe painful sunburn, often accompanied by bullae on the erythematous areas. The pain and erythema continue 1 to 3 days after exposure and is then replaced by moderate marked pigmentation of the skin. Actual contact with creosote is not necessary for the production of a photosensitive reaction, since the vapor released from creosote in the presence of sunlight can produce a photodermatitis (4). There may be a latent period of two weeks or more between initial exposure to creosote or its vapors and the appearance of photosensitivity. The amount of pigmentation normally in the skin dictates a person's susceptibility to photodermatitis. Fair skinned individuals are at the highest risk, while dark skinned races, such as blacks and Indians are almost immune (4).

The ultimate response to long-term, dermal exposure to creosote is cancer. Creosote is a recognized carcinogen capable of producing skin

cancer of the hands, forearms, face, neck, scrotum and penis (5). The carcinogenic potential of creosote has been well documented, both in laboratory animals and in humans (8,9,10,11). An extensive search for the carcinogenic fraction in creosote has been carried out without success. Early investigations linked the presence of benzpyrene in creosote to its carcinogenic potential, however, the work of Lijinsky, *et al.* (11) stresses the fact that the amounts of benzpyrene in creosote are not adequate to account for the biological activity that creosote exhibits. Therefore, it is believed that creosote must either possess more than one carcinogenic fraction, or a component that has a promoting action on the carcinogenic capability of benzpyrene. In addition to this phenomenon, known as cocarcinogenesis, the symptomology of creosote induced cancer is a multistaged sequence. The first stage in the sequence is the appearance of a benign papilloma known as "tar-wart", that possesses the ability to regress. This develops into a localized malignant papilloma, and only then will the disease progress into the final stage of an invasive epithelioma (10). This finding is encouraging, making early detection of pre-malignant tumors a control for the cancers caused by chronic dermal exposure to creosote. The affinity of creosote to be carcinogenic may not end with the skin. Recent evidence indicates that creosote may also have the ability to promote lung cancer. Although experimental and epidemiological data concerning the carcinogenicity of inhaled creosote vapor is lacking, creosote is known to be concentrated in the lung for excretion from the body. Retention time in the lung is not known, but it may be sufficient to produce tumors (1,5).

In conclusion, the chronic toxicity of creosote is of an extremely high order. The dermal route of exposure is most significant because of

the carcinogenic and phototoxic capabilities of the chemical. However, chronic intoxication can take place from repeated ingestion of creosote, and the respiratory route of exposure may become immediately significant if in fact creosote becomes a recognized carcinogen of the lung.

VI. Environmental Toxicology:

Very little is known of the environmental toxicology of creosote. What information is available tends to incriminate creosote as a very persistent environmental compound, as well as one able to exert some toxic action in the environmental ecosystem. Creosote has long been used as a wood preservative because of its ability to withstand the elements for long periods of time. Telephone and electrical utility poles coated with creosote still retain a considerable portion of the chemical after periods of 25 to 30 years (1). From this fact it seems evident that the biodegradability of creosote is extremely low, making this compound an extremely persistent environmental chemical. In addition to the ability of creosote to remain within the environment, it exhibits toxic action on at least one biological system in the environment, that being aquatic life. The 1975 Registry of Toxic Effects of Chemical Substances assigns an aquatic toxicity value (TL_m 96) to creosote of 1 to 10 ppm. This means that 1 to 10 ppm of creosote in water will kill 50 percent of the aquatic test organisms in 96 hours, making creosote a moderate toxin to aquatic life.

In an occupational environment, creosote is known to be the cause of eye injury, respiratory irritation, photodermatitis, and skin cancer (1,4,5,7). Steps can be taken in the industrial environment to minimize the dangers of contact with creosote including adequate ventilation, use

of goggles and rubber gloves, daily laundering of impregnated clothing, thorough cleaning of all exposed body parts at the end of a work period, and frequent medical examination to detect skin disorders in their early stages (1,10).

From a safety standpoint creosote presents hazards. The compound is readily flammable and burns with a luminous, smoky flame. In addition, creosote possesses the relatively low flash point of 165°F. Since the proposed solar heating and cooling system will operate at internal temperatures of 200°F, the possibility of flammable concentrations of creosote vapors being generated appears highly possible. If the possibility of combustion of creosote vapors within the system exists, or if the vapors could potentially escape from the unit, the use of creosote as a heat transfer medium is undesirable from a safety standpoint.

VII. Recommendations:

In view of the toxicological and safety information currently available, the use of Creosote Coal Tar as a heat exchange medium for solar heating and cooling is not recommended. The ability of this compound to cause a wide range of physiological disorders in both animals and man is well known, and its recognized carcinogenic potentials should immediately eliminate consideration of creosote in a solar heating and cooling system that may find widespread private and commercial use. In addition, creosote seems to be extremely persistent in the environment where it also exhibits some toxic effect on aquatic life. All of the toxicological and safety information now available on creosote indicates that further consideration of this compound as a heat exchange medium is highly undesirable.

References

1. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
2. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
3. Sax, N.I. Dangerous Properties of Industrial Materials: Fourth Edition. Litton Educational Publishing Inc. New York. 1975.
4. Fisher, A.A. Contact Dermatitis. Lea and Febiger. Philadelphia, Pennsylvania. 1967.
5. Hueper, W.C. and W.D. Conway. Chemical Carcinogenesis and Cancers. Charles C. Thomas - Publisher. Springfield, Illinois. 1964.
6. Taylor, J.M., *et al.* A Comparison of the Toxicity of Some Allyl, Propenyl, and Propyl Compounds in the Rat. Toxicology and Applied Pharmacology. Vol. 6. pp. 378-387. 1964.
7. Birdwood, G.T. Keratitis from Working with Creosote. British Medical Journal. Vol. 2. page 18. 1938.
8. Cabot, S., *et al.* Development of Skin Tumors in Mice Painted with 3,4-Benzpyrene and Creosote Oil Fractions. American Journal of Pathology. Vol. 16. pp. 301-132. 1940.
9. Sall, R.D. and M.J. Shear. Effect of the Basic Fraction of Creosote Oil in the Production of Tumors in Mice by Chemical Carcinogens. U.S. National Cancer Institute Journal. Vol. 1. pp. 45-55. 1940.
10. Poel, W.E. and A.G. Kammer. Experimental Carcinogenicity of Coal Tar Fractions: The Carcinogenicity of Creosote Oils. U.S. National Cancer Institute Journal. Vol. 18. pp. 41-50. 1957.
11. Lijinsky, W., *et al.* A Study of the Chemical Constitution and Carcinogenic Action of Creosote Oil. U.S. National Cancer Institute Journal. Vol. 18. pp. 687-692. 1957.

TOXICOLOGICAL EVALUATION OF ACETYLENE TETRABROMIDE

September 9, 1976

ABSTRACT

Acetylene tetrabromide, more commonly referred to as tetrabromoethane (TBE), is a member of a large chemical family known as the aliphatic halogenated hydrocarbons. Because of its high density, TBE has found industrial use as an ore flotation agent, a gauge fluid, in balancing equipment, and as a special solvent. The toxic properties exhibited by TBE are characteristic of the aliphatic halogenated hydrocarbon family. It is primarily a central nervous system depressant, with the ability to injure the tissues of the lungs, liver, and kidneys. Experience with both experimental animals and man has shown the respiratory route of entry to be of most significance from both acute and chronic exposure. Inhalation of small quantities of TBE can lead to narcosis that can end in respiratory collapse and death, as well as significant injury to the lungs, liver, and kidneys. The environmental toxicology of TBE is not known, and in the industrial setting, TBE can be effectively controlled primarily because of its low vapor pressure at ambient atmospheres. However, at sufficiently high conditions of temperature and pressure, TBE vapor can be generated in amounts great enough to induce intoxication.

In view of the toxicological information currently available, acetylene tetrabromide is not recommended for use as a heat transfer medium for solar heating and cooling.

I. Chemical Properties:

Name: acetylene tetrabromide

Molecular formula: $\text{CHBr}_2 \text{CHBr}_2$

Synonyms (1): 1,1,2,2 - Tetrabromoethane; Tetrabromoethane;
Tetrabromoacetylene; s - Tetrabromoethane; Muthmanns Liquid;
TBE

Molecular weight (2): 345.67

Freezing point: 32°F, 0°C

Boiling point (2): 462°F

Flash point (3): Acetylene tetrabromide has no flash point.

Specific gravity (2): 2.9656

Refractive index (2): $n_D = 1.6353$ @ 20°C

Vapor density (3): 11.92 (air = 1)

Solubility (2): 0.065 g per 100 ml water @ 30°C; soluble in
alcohol, ether, acetic acid, acetone, benzene, chloroform

Physical state (3): colorless to yellow liquid

II. Hygienic Standards:TLV: air 1 ppm (approximately 14 mg/m³)

(OSHA Standard 1910.93) and (ACGIH 1971)

III. General Toxicology:

Acetylene tetrabromide, more commonly referred to as tetrabromo-
ethane (TBE), is one of many compounds classified as the aliphatic halogenated

hydrocarbons. The members of this chemical family are among the most widely available and used industrial chemicals. Because of their excellent solvent properties, the aliphatic chlorinated compounds account for most of the industrial usage of halogenated hydrocarbons, followed by the fluorinated compounds, the bromine containing organics, and finally the iodine derivatives (4). TBE is the tetrabrominated derivative of ethane, formed by the action of bromine on acetylene. Because of its high density, TBE has found industrial application as an ore flotation agent, a gauge fluid and in balancing equipment. In addition, it has some use as a special solvent (3).

Because of their chemical diversity, it is difficult to generalize the toxicology of the aliphatic halogenated hydrocarbons. However, some physiological responses are more common from exposure to these compounds than others. From a single acute exposure, the most common response is narcosis. The degree of central nervous system depression exhibited, however, can range from deep anesthesia to weak inebriation (3). In addition, many of the halogenated hydrocarbons are known to potentiate adrenalin. In severe cases of acute poisoning, cardiac arrhythmia may occur from production of endogenous adrenalin, hence adrenalin should not be administered to a person who has has a serious exposure to halogenated hydrocarbons (3). The physiological effects of chronic exposure to halogenated hydrocarbons are even more varied. Many of these compounds, however, show a particular affinity for the tissues of the liver and kidney where severe injury may take place (3).

TBE exhibits a toxicology almost identical to that which is considered typical for the aliphatic halogenated hydrocarbons. It is primarily a central nervous system depressant that may cause narcosis and coma, and eventually

death from respiratory failure. In addition, it is an irritant of the lung and pathological changes can be observed in the liver and kidneys (3).

IV. Acute Toxicity:

Acute toxicity data is available for exposure to TBE from all routes of entry. Oral administration of TBE to laboratory test animals has established an LD₅₀ value of 0.4 g/kg for rabbits and guinea pigs. Similar studies show that rats survive a single oral dose of TBE at 0.6 g/kg, but doses of 1.6 g/kg are fatal (1,3).

Although the oral toxicity data for TBE indicates its potential to be fairly toxic, the route of exposure which is of most concern is the respiratory one. Acute intoxication by TBE via inhalation shows that the chemical is a strong central nervous depressant and capable of causing liver and kidney injury. Experimental animals exposed to vapors of TBE at near saturation show signs of narcosis after a short period of time. Rats lose consciousness in 3 hours, rabbits show the same effect in 2 1/2 hours, and guinea pigs will be anesthetized in 1/2 hour. Guinea pigs exposed 1 1/2 hours or more regain consciousness, but die in periods of 1 to 5 days, with signs of injury to the liver and kidneys (3,5). The potential of TBE to be acutely toxic has also been documented in humans. A chemist who had worked with TBE for only one day suffered a case of near fatal intoxication with liver injury the predominant pathological finding. He was exposed to concentrations of 2 ppm TBE in air, with a peak exposure of 16 ppm for approximately 10 minutes. Other workers in the area complained of irritation of the eyes and nose, followed by headache and lassitude (5).

The toxic potential of TBE from dermal exposure is not clear. It has not yet been determined if the chemical has the ability to be absorbed

through intact skin, and there have been no reports of skin sensitization to TBE. The chemical is, however, capable of producing dermatitis. TBE applied to the skin by a patch test will produce a slight redness that leads to edema and blistering in 24 hours (3).

In conclusion, the acute toxic potential of TBE is of a relatively high order. The compound is a strong anesthetic, especially when inhaled in its vapor form. Experience in laboratory animals and man also indicates that single acute exposures to TBE can produce significant injury in the liver and kidneys. For these reasons, an extremely low TLV of 1 ppm TBE in air has been established for this chemical (5).

V. Chronic Toxicity:

Data concerning the ability of TBE to be chronically toxic is only available for respiratory exposure. Chronic oral exposure to TBE is generally considered to present only minimum toxicological danger, and the role of dermal exposure in the chronic toxicology of the chemical is as yet undetermined (5). However, experimental animals chronically exposed to TBE vapors and aerosols have shown signs of intoxication at relatively low concentrations. In a study performed by the Dow Chemical Company and cited by Patty (3), rats, guinea pigs, rabbits, and a monkey were exposed to concentrations of 14 ppm, 4 ppm, and 1.1 ppm TBE in air for periods of up to 190 days. At the highest concentrations, all animals suffered histopathological changes in the liver and lungs, as well as increases in liver weight. At 4 ppm the same changes were observed in the liver and lungs. Only at 1.1 ppm did the test animals appear to remain normal (3). In addition to these findings, guinea pigs have shown the ability to withstand 15 minutes per day exposures of air saturated with TBE vapor without cumulative effects (5). Finally, the ability of TBE to be chronically toxic when

vaporized also applies when the chemical is dispersed as an aerosol. Rats exposed daily to aerosol concentrations ranging from 3.7 to 4.2 mg/liter for 2 hour periods died within a relatively short period of time (3).

In conclusion, intoxication from chronic respiratory exposure to TBE seems highly probable, especially to the tissues of the lungs and the liver. In addition, the possibility of dermal absorption of TBE should be considered as potentially toxic until more toxicological research is conducted on this route of entry.

VI. Environmental Toxicology:

The action of TBE on the environment is not known. To date, no studies assessing the biodegradability of the compounds or its potential to biomagnify in the food chain could be found.

In the industrial environment, TBE can be toxicologically controlled without difficulty. The chemical has a very low vapor pressure at ambient temperatures and pressures, therefore overexposure from inhalation is not generally expected (4). However, if TBE is used at high temperatures, the possibility of generating vapors in sufficient concentration to be toxic is great. Under these conditions, adequate ventilation at the source of exposure is essential. In addition, sound industrial hygiene practice should be followed when using TBE, including immediate thorough washing of TBE from exposed skin surfaces, regular laundering of work clothes, and medical surveillance of exposed individuals.

VII. Recommendations:

On the basis of toxicological information currently available, acetylene tetrabromide is not recommended for use as a heat transfer

medium for solar heating and cooling. Sufficient evidence in both experimental animals and man proves this chemical to be relatively toxic from acute as well as chronic exposure. The compound has the ability to cause severe central nervous depression that can lead to respiratory collapse, and it is capable of injuring the tissues of the lungs, liver, and kidneys at extremely low concentrations. Although under normal conditions the chemical can be easily handled, the internal operating temperatures of the proposed solar system would be sufficiently high to produce toxic concentrations of TBE vapor. For these reasons, TBE is not toxicologically acceptable as a heat transfer medium.

References

1. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
2. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
3. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
4. Hamilton, A. and H.L. Hardy. Industrial Toxicology. Publishing Science Group, Inc. Acton, Massachusetts. 1974.
5. American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values. Third edition. Cincinnati, Ohio. 1974.

TOXICOLOGICAL EVALUATION OF CRESYL DIPHENYL PHOSPHATE

June 24, 1976

ABSTRACT

Cresyl diphenyl phosphate belongs to a family of chemical compounds known as phosphate esters, widely used industrially as plasticizers. The toxicology of this chemical is vague because of a lack of data in this area. Considered by some to be almost inert toxicologically, others compare it to its highly toxic chemical relative tri-o-cresyl phosphate (TOCP). Limited data available on the acute toxicity of cresyl diphenyl phosphate shows it to be of the same magnitude toxicologically as TOCP. The ability of the chemical to produce paralysis is questioned. The chronic, environmental, and industrial toxicologies of cresyl diphenyl phosphate are not known.

Due to the scarcity of toxicological data currently available, and the possibility that cresyl diphenyl phosphate may exhibit a toxicity similar to that of TOCP, the chemical is not recommended for use as a heat exchange medium for solar heating and cooling.

I. Chemical Properties:

Name: Cresyl Diphenyl Phosphate

Molecular Formula: $(\text{CH}_3\text{C}_6\text{H}_4)(\text{C}_6\text{H}_5)_2\text{PO}_4$

Molecular weight: 337.0

Freezing point: -36°F

Boiling point: 734°F

Flash point: 450°F

Specific gravity: 1.208

Vapor pressure: 5.0 mm Hg @ 220°C (1)

Solubility: H_2O (g/100ml) - Insoluble (1)

II. Hygienic Standards:

There are presently no available standards for exposure to cresyl diphenyl phosphate.

III. General Toxicology:

Cresyl diphenyl phosphate is a member of a group of chemical compounds known as phosphate esters. More specifically, cresyl diphenyl phosphate is considered to be a tri-aryl phosphate, a specific group of esters used widely in industry as plasticizers. Along with its plasticizing properties, cresyl diphenyl phosphate imparts a flameproofing effect to finished products. Cresyl diphenyl phosphate is used as a plasticizer for polyvinyl chloride, cellulose acetate, cellulose acetobutyrate, and cellulose acetopropionate (2).

As a group, the phosphate esters show an extreme diversity toxicologically. A study of the physiological properties of the phosphate esters shows that they can generally be described as having five major

types of toxic effects. They are:

1. Damage to the central nervous system with resultant flaccid or spastic paralysis.
2. Stimulation of the nervous system or convulsive effects, or in some cases an anesthetic like action.
3. Depression of true or pseudocholinesterase with the latter predominating.
4. Irritant action on skin and respiratory surfaces.
5. No major toxic effects (1).

The toxicology of many of the phosphate esters, specifically tri-o-cresyl phosphate (TOCP) is well known and well documented. However, available information on cresyl diphenyl phosphate is at best sketchy. Patty (1) places cresyl diphenyl phosphate in the category "No major toxic effects" and labels it as almost inert. However, both Lefaux (2) and Sax (3) compare cresyl diphenyl phosphate toxicologically to TOCP, the most toxic of all plasticizers, capable of producing permanent paralysis and central nervous system dysfunction in humans and animals upon exposure to relatively small quantities of the chemical.

IV. Acute Toxicity:

What little toxicological data is available for cresyl diphenyl phosphate is on the chemical's acute effects in animals. Only two studies could be found, one cited by Patty (1), conducted by Eastman Kodak Company that had been previously unpublished, and the second by Mallette and Von Haam (4). The results of these two studies, expressed as LD₅₀ values, are summarized in Table I.

Table I.

Acute toxicity data for cresyl diphenyl phosphate.

<u>Animal</u>	<u>Route of Exposure</u>	<u>LD₅₀ (g/kg)</u>
Rat	Oral	4.0*
	Oral	6.4 - 12.8
	Intraperitoneal	1.0*
Mouse	Oral	6.4 - 12.8
Guinea Pig	Oral	1.6 - 3.2

* Values from reference (4), all others from reference (1).

In the study cited by Patty (1), no signs of paralysis were found in any of the test animals, but some dyspnea did appear at high dosages. Mallette and Von Haam (4) report that poisoned animals became lethargic on the second or third day, followed by copious diarrhea and symptoms of paralysis. Autopsy showed a general capillary paralysis accompanied by oedema and cerebral hemorrhage.

The Eastman Kodak study also tested the acute effects of cresyl diphenyl phosphate from dermal exposure. Tests with guinea pigs showed that the chemical was not a skin irritant, nor was it absorbed through the skin (1). The acute toxic effects of inhalation of cresyl diphenyl phosphate are not known. However, the low vapor pressure of the ester is a source of protection from respiratory exposure (5).

In conclusion, the oral route of exposure seems to be most significant in terms of acute toxic effects. The LD₅₀ values reported for oral exposure are generally of the same magnitude of those given for the highly toxic TOCP. There is some evidence that cresyl diphenyl phosphate may also have the ability to cause paralysis as does TOCP. Although the

dermal and respiratory routes of exposure appear insignificant, sufficient data does not exist to conclude that acute effects cannot be caused via skin contact and inhalation. It must be noted that the data that is available is for laboratory test animals. The acute toxic effects of cresyl diphenyl phosphate on humans are not known.

V. Chronic Toxicity:

To date, the chronic health effects caused by exposure to cresyl diphenyl phosphate have not been evaluated. There currently exists no experimental data on the chronic toxicity of the chemical in animals or in man. To obtain some understanding of how cresyl diphenyl phosphate might act chronically, a comparison can be made between it and TOCP. Although not conclusively proven, it has been shown that TOCP may have a cumulative effect in the body. Using chickens, Smith et al. (6), have shown that repeated exposure of subtoxic doses of TOCP will eventually produce the paralytic syndrome typical of acute TOCP poisoning. There is some evidence to support the hypothesis in humans from long-term, low-level exposure in the industrial environment. Paralysis has been documented in workers that have experienced dermal and respiratory exposure to TOCP (1). Because there is a possibility that TOCP accumulates in the body, plus the fact that the chemical is absorbed through the skin, TOCP is generally regarded as having a high order of chronic toxicity. Since cresyl diphenyl phosphate is compared toxicologically to TOCP, it should be assumed that cresyl diphenyl phosphate also possesses a high order of chronic toxicity.

VI. Environmental Toxicology:

The action of cresyl diphenyl phosphate in the environment is not

known. No information currently exists that describes the ability of the chemical to biodegrade, or its potential to be biomagnified in the food chain. Since the environmental toxicology of none of the phosphate ester plasticizers has been defined, it is impossible to predict the effects that increased usage of cresyl diphenyl phosphate would have on the environment.

Essentially nothing is known of the industrial toxicology of cresyl diphenyl phosphate. Although widely used industrially, there have been no reported cases of cresyl diphenyl phosphate poisoning in the workplace. However, the possibility that this chemical may exhibit a toxicology similar to that of TOCP should be noted, and proper care when using cresyl diphenyl phosphate in the industrial environment should be taken. From the standpoint of occupational safety, cresyl diphenyl phosphate presents little hazard. The danger of fire or explosion is slight when the chemical is exposed to heat or flame and any fire that does occur can be extinguished with water or chemically. Caution should be taken, however, when the chemical is under intense heat. If heated to decomposition, highly toxic vapors of phosphorus oxide are emitted (3).

VII. Recommendations:

Based on the fact that minimal toxicological literature exists on cresyl diphenyl phosphate, and the possibility that it may act toxicologically like its chemical relative TOCP, cresyl diphenyl phosphate is not recommended for use as a heat exchange medium for solar heating and cooling. Although the chemical has not actually been proven to have a high order of toxicity, the risk of using it under the assumption that it is not as toxic as believed is great. Other chemicals have been extensively researched and determined toxicologically safe. These chemicals

should be strongly considered and used, in favor of cresyl diphenyl phosphate whose toxicological background is at best vague.

References

1. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons, Inc. New York. 1967.
2. Lefaux, René. Practical Toxicology of Plastics. Iliffe Book Ltd. London, England. 1968.
3. Sax, N.I. Dangerous Properties of Industrial Materials. Litton Educational Publishing Inc. New York. 1975.
4. Mallette, F.S. and E. Von Haam. Studies on the Toxicity and Skin Effects of Compounds Used in the Rubber and Plastics Industries. I: Accelerators, Activators, Antioxidants. Arc. Ind. Hyg. Occup. Med. Vol. 5, No. 4. pp. 311-317. April, 1952.
5. Hamilton, A. and H.L. Hardy. Industrial Toxicology. Publishing Science Group, Inc. Action, Massachusetts. 1974.
6. Smith, M.I., et al. Further Studies on the Paramocology of Certain Phenol Esters With Special Reference to the Relation of Chemical Constitution and Physiologic Action. NIH Bulletin. No. 160. pp. 1-53. August, 1932.

TOXICOLOGICAL EVALUATION OF TRI-O-CRESYL PHOSPHATE

June 30, 1976

ABSTRACT

Tri-o-cresyl Phosphate (TOCP) belongs to a family of compounds known as phosphate esters and is more specifically a tri-aryl phosphate. TOCP is used industrially in many ways, but finds most use as a plasticizer. Toxicologically, TOCP exhibits a high order of both acute and chronic toxicity. Of most concern is the ability of the chemical to cause a permanent paralytic condition from the ingestion of relatively small doses of TOCP. There is also evidence that TOCP can be absorbed through human skin, and that it may have the ability to accumulate in the body making long-term, low-level exposure as dangerous as acute exposure. In spite of its potent toxic effects, reported cases of TOCP poisoning resulting from occupational exposure are relatively few. This is attributed to stringent controls practiced in the industrial environment. No data currently exists on the persistence of TOCP in the environment.

On the basis of toxicological information currently available, TOCP is not recommended for use as a heat exchange medium for solar cooling and heating.

I. Chemical Properties:

Name: Tri-o-cresyl Phosphate

Molecular Formula: $(\text{CH}_3 \text{ C}_6 \text{ H}_4)_3 \text{ PO}_4$

Molecular weight: 368.37 (1)

Synonyms: Tricresyl phosphate, tritolyl phosphate, o-tolyl phosphate, tri-o-tolyl phosphate, TCP, TOCP, TOTP (2)

Freezing point: -13°F Boiling point: 770°F , 410°C (3)Flash point: 437°F Auto-ignition point: 725°F

Specific gravity: 1.162

Viscosity (CSTKS): 60 @ 25°C (4); 4.0 @ 100°C Refractive index: $n_D = 1.5575$ @ 20°C (1)Vapor pressure: .0001 @ 20°C (4); 0.1 @ 155°C (5); 0.25 @ 170°C (5); 0.5 @ 185°C (5); 10.0 @ 200°C (5)

Solubility: water - insoluble (1); alcohol - very soluble (1); ether - very soluble (1)

Appearance: colorless to pale yellow liquid (1)

At 25° and 760 mm Hg: 1 ppm = 0.01505 mg/liter (3)

1 mg/liter = 66.44 ppm

II. Hygienic Standards:

TLV: Air 0.1 mg/m^3 (OSHA Standard 1910.93) and (ACGIH 1971)

This chemical may be absorbed through the skin.

III. General Toxicology:

Tri-o-cresyl phosphate (TOCP) is a member of a group of chemical compounds known as phosphate esters. More specifically, TOCP is a tri-aryl phosphate, all of which have considerable industrial importance. As a commercial product, TOCP is synthesized by the interaction of phosphorous oxychloride on mixtures containing phenol and all isomers of cresol, xylenol, and some higher molecular weight tar acids (4). By far, TOCP is used most widely in industry as a plasticizer. Because of its very general solvent and plasticizing properties this type of plasticizer is used in considerable amounts in both varnishes and plastics. TOCP is among the plasticizers of choice for polyvinylchloride and is an excellent softener for nitrocellulose. Along with its plasticizing capabilities, TOCP also contributes fireretarding properties to the finished products (5). In its other industrial applications, TOCP is used as a gasoline additive, as a recovery agent for phenols in coke-oven plants, in transformers, and as a machine and aviation lubricant because of its relatively wide temperature range (4).

Toxicologically, the phosphate esters display a wide range of physiological response, and to generalize their toxicity is difficult. The phosphate plasticizers, as a whole are considered to be toxic, and are clearly the most toxic of all chemical compounds used as plasticizers (4). Based upon study of their physiological properties, the phosphate esters can generally be placed in one or more of the following categories of toxic effect:

1. Central nervous system damage with resultant flaccid or spastic paralysis.
2. Stimulation of the nervous system or convulsive effects or in some cases an anestheticlike action.
3. Depression of true or pseudocholinesterase production with the latter predominating.
4. Irritant action on skin and respiratory surfaces.
5. No major toxic effects (5).

The degree of toxicity that the phosphate esters exhibit is directly related to chemical structure. The most toxic configurations are the orthoisomers of the esters, while the meta and para isomers are basically nontoxic (3,6).

TOCP, being the ortho isomer of tricresyl phosphate, is considered to be the most dangerous of all phosphate ester plasticizers toxicologically, and falls in categories one and three above. Because of its low vapor pressure, the respiratory route of exposure is generally considered to be insignificant, but should not be neglected at higher temperatures. The oral and dermal routes of exposure are considered to be the most dangerous since ingestion of the compound exerts dramatic toxic action and it is readily absorbed through the skin (3,7).

IV. Acute Toxicity:

Much is known about the acute toxicity of TOCP in both animals and man. Great interest was shown in the chemical after a human poisoning epidemic in 1930. From that incident, which will be covered in subsequent areas of this paper, evolved much data on the acute toxicity of TOCP via animal studies. Although this data is over forty years old, and

expressed as Minimum Toxic and Lethal Doses, rather than the more common LD₅₀ value, it is still considered valid and accurate. This data is summarized in Table I.

TABLE I.
Acute Toxicity Values for TOCP.*

<u>Animal</u>	<u>Route of Exposure</u>	<u>Minimum Toxic Dose</u>	<u>Minimum Lethal Dose</u>
Rabbit	Oral	50 mg/kg	100 mg/kg
	Intravenous		75 mg/kg
Rat	Subcutaneous		500 mg/kg
Chicken	Oral	0.3 g/kg	0.4 g/kg
Monkey	Subcutaneous		1 cc/kg
Dog	Subcutaneous		0.4 - 1.6 cc/kg

* All values are from reference (8), except the monkey and dog data are from reference (9).

In addition to these early values, more recent LD₅₀ values are given by Patty (5) and are listed in Table II.

TABLE II.
Approximate LD₅₀ Values for TOCP.

<u>Animal</u>	<u>Route</u>	<u>LD₅₀ (g/kg)</u>
Rat	Oral	3 - 10
Cat	Subcutaneous	0.1 - 0.2
Chicken	Oral	0.1 - 0.2
Mouse*	Intraperitoneal	0.28 cc/kg

* Mouse data is from reference (10).

All of the values cited indicate that the acute toxicity of TOCP in animals is of a high order. Death comes quickly, from a few minutes to a number of hours, depending on the species of animal. A few of the animal types tested, most predominantly the rat, show some resistance to TOCP. Their lower susceptibility is due to a slow, incomplete absorption of TOCP, but even in these resistant strains the strong toxic action of TOCP is soon evident (8). The lethality of TOCP is of not as much concern as the chronic syndrome that it produces upon exposure to sub-lethal doses. In all animals tested, application of sub-lethal doses of TOCP in any manner caused a severe paralysis of the extremities and was seldom followed by recovery and usually resulted in death (8,9,11).

The physiological response in humans to TOCP is generally the same as that in animals. However, in man, TOCP is rarely lethal, although it is estimated that an oral dose of 1.0 g/kg can cause death (7). The more prominent syndrome, and the one that causes most concern, is a neuromuscular disturbance characterized by flaccid paralysis, from which recovery is slow, or with permanent disability. This disease, commonly known as "Jake paralysis" or "Ginger paralysis", was first outlined by Smith, et al., (8,9) in their classic epidemiological investigation of the human poisoning epidemic of 1930. At that time, many people in the southeastern United States fell prey to a strange type of paralysis that afflicted the upper and lower extremities, the etiological agent of which was unknown. The epidemiologic pattern over which the disease spread and the syndrome produced eliminated infectious agents from consideration. An extensive search by Smith, lead to only one common denominator among those afflicted with the paralysis, consumption of a ginger extract sold as a flavoring agent for cooking, but consumed during Prohibition days for its alcoholic content.

Chemical analysis of the suspected ginger extract turned up concentrations of TOCP in amounts as large as 2%. Once TOCP became suspect, Smith produced the paralytic syndrome in test animals, both with the adulterated ginger and pure TOCP, thus confirming TOCP to be the causative agent of the disease.

Since that first discovery of the toxicological properties of TOCP, numerous other poisonings in man have been documented, including the most recent epidemic in Morocco in 1959 (12). In that outbreak, more than 10,000 people were afflicted from the use of cooking oil that was adulterated with aviation lubricating oil containing TOCP. Permanent paralysis was the result in some 10 to 15 percent of these cases (13).

The symptomology of TOCP poisoning is fairly consistent from case to case and has been well described. Most often, the onset of symptoms, which are chronic, are triggered by one acute dose or exposure. Shortly after exposure, usually ingestion, there may be, but not always, gastrointestinal disturbance including nausea, vomiting, diarrhea, and abdominal pain. Remission of these early symptoms is followed by a symptom free interval of 3 to 28 days, dependent upon the total dose and the period of time over which exposure had taken place (3,9,11). First signs of peripheral polyneuritis appear as sharp, cramplike pain in the calves with some numbness in the hands and feet. In a few hours, increased weakness in the hands and feet become apparent and bilateral footdrop develops. In a few days, there may be progression to involve the fingers or wrists. This process does not seem to extend above the elbows, and the larger muscles of the thigh are only infrequently involved. Sensory loss, if it is to occur at all, will be evident by this time. Muscular weakness may increase over a period of several weeks or even months and then become more or less stationary. The time of

recovery can be several years, but the prognosis is poor. Although some paralytics recover completely, and others improve sufficiently to be rehabilitated, the majority of victims never regain normal function of the central nervous system, and 25 to 30 percent of those afflicted will remain permanently disabled (3,5,9,11,14).

The pathological changes caused by TOCP poisoning are well known and are essentially the same in man and animal. The multiple neuritis of this paralysis is essentially a demyelination of the peripheral nerves and particularly in the spinal cord. Degenerative changes in the anterior horn cells throughout the spinal cord are visible, but most often this damage is seen in the lumbar and cervical regions (5,6,15). The exact mechanism of toxicity of TOCP is still not determined. The early theories credited the demyelination to the ability of TOCP to inhibit cholinesterase and pseudocholinesterase. If in fact this were the case, TOCP would have a mode of action similar to the organophosphate insecticides. However, many pathological studies on both animals and humans have shown that the demyelination is not solely or directly related to the activity of TOCP as an inhibitor of cholinesterase (6,15).

As indicated, the most feared route of exposure to TOCP in man is that of ingestion. Although the exact toxic dose has never been decided, serious paralysis has been produced in man by an oral dose of 6-7 mg/kg, even though estimates of 10-30 mg/kg are considered to be more valid (3,5). Although the probability of obtaining acute toxic effects from TOCP via the dermal and respiratory routes is extremely low, they should not be disregarded. A 1932 industrial mishap with TOCP ended in death for one worker when his body was heavily splashed with a crude distillate of TOCP. The skin that came into contact with the chemical was

severely burned and symptoms of vomiting, haematuria, and anuria set in immediately. Death was attributed to kidney failure caused by fatty degeneration of the renal epithelium (4). Similar acute episodes caused by inhalation of TOCP vapors have not as yet been documented. However, one respiratory study has been done with laboratory animals. Cats were exposed to an atmosphere containing 2.7 mg TOCP vapor per liter of air for seven hours. At first, the animals were restless, but after six hours apathy supervened. Some mucous membrane irritation was apparent (4).

In conclusion, the acute toxicity of TOCP is of an extremely high order. Of most concern is the long term paralysis that results from dosages of a fairly low order of magnitude. The oral route of exposure presents the most hazard from an acute standpoint, but exposure to high concentrations of TOCP dermally or via the respiratory tract can produce violent toxic reactions.

V. Chronic Toxicity:

In contrast to the wealth of information that exists on the acute toxicity of TOCP, little is available on the chronic effects. What is in the literature is mainly speculative rather than confirmed. The biggest question that still remains unanswered is the ability of TOCP to accumulate in the body. Although never shown in man, there is some evidence which indicates that TOCP may have a cumulative effect. Smith, et al. (8) have exposed chickens to repeated ingestions of subtoxic doses of TOCP. This daily ingestion of ineffective doses over a period of days gave rise to the paralysis characteristic of TOCP poisoning as the total dose approached the minimum paralyzing dose. In addition to this finding that hints that the long term effects of TOCP poisoning may be as severe

as the acute effects, is the proven ability of TOCP to be absorbed through human skin. Hodge and Sterner (10) applied small quantities of TOCP, labeled with radioactive phosphorus, to the palms of two human subjects. After a 3 1/2 hour exposure to doses of .22 and .11 grams, the chemical was removed. The results of the test were striking. Within one hour of application, large amounts of TOCP were already appearing in the bloodstream. Twenty-four hours after application, an average of 8 mg of TOCP per 100 c.c. of blood was found. Urinary excretion of the compound began almost as rapidly as uptake did, but only 0.1 and 0.4 percent of the total dose applied was excreted. These results indicated that TOCP was not only readily absorbed through the skin, but may remain in the body in some proportion. An added danger is the fact that while TOCP is absorbed through the skin, the chemical is not an active primary skin irritant, nor does it produce cutaneous sensitization, so that individuals coming in contact with the material would judge it to be innocuous (5,10).

All of these findings indicate that TOCP may be just as toxic on a chronic level of exposure as it is on an acute level. Long-term, low-level exposure to TOCP orally, dermally, or via respiration, or in combination seems to have the ability to produce clinical syndromes similar to those of acute exposure. Studies following workers exposed to TOCP in industrial environments over long periods of time lend some proof to this hypothesis. Although some of these studies list no chronic effects other than a 70 percent drop in plasma cholinesterase, other studies list chronic effects including hyperhidrosis, hypotension, fatigue, affective irritability, paraesthesia in the limbs, and permanent paralysis (4,5).

Although conclusive data is not currently available to confirm the high order of chronic toxicity, all indications are that TOCP may be as dangerous over long periods of low-level exposure as it is in acute exposure.

VI. Environmental Toxicology:

The action of TOCP in the environment is not known. Currently, there is a complete lack of information regarding the chemicals biodegradability, its ability to persist in soils and water, and the possibility that it may magnify in the food chain. Several studies have indicated that TOCP may be persistent in animals and man which leads to the speculation that the chemical may also be environmentally persistent. However, no environmental investigations have been conducted to support or discredit this hypothesis.

TOCP presents more hazards toxicologically than any other plasticizer currently in use, especially to those occupationally exposed. In spite of its extensive industrial use, there have been relatively few reports of acute or chronic TOCP poisoning. This can only be attributed to the practice of good control procedures. When attempting to control TOCP in the industrial environment, the following practices should be required (3,10,14):

1. Adequate ventilation
2. Chemical goggles
3. Mechanical filter respirator
4. Long-sleeve coveralls with tight collars and cuffs that are laundered daily
5. Gloves and boots

6. Avoid generation of mist, fog, or aerosol.
7. Immediate removal of spills from skin with soap and water.
8. Thorough washing of hands and other exposed body parts at the end of the work day.
9. No smoking, eating, or drinking in the work area.
10. Preplacement of employees, precluding from exposure those individuals with central nervous system disease.
11. Weekly determinations of cholinesterase levels in workers.
12. An intensive worker education program to familiarize employers with the dangers involved with working with this chemical.

VII. Recommendations:

From a toxicological standpoint, TOCP is not recommended for use as a heat exchange medium for solar heating and cooling. The chemical has a long history of causing adverse health affects among human as well as animal populations. Of most concern is the ability of the chemical to cause permanent paralysis and central nervous system damage from one relatively small dose regardless of the route of exposure. This high order of acute toxicity makes TOCP a most unfavorable component of a heating and cooling unit that may be widely used in private homes and businesses.

In addition to TOCP's potent acute effects, there is evidence to support the hypothesis that the chemical can accumulate in the body, making long-term, low-level exposure as dangerous as acute exposure. The lack of knowledge concerning the persistence of TOCP in the environment also discourages the use of this chemical as a heat exchange medium.

In conclusion, it is strongly recommended that other chemicals

that have been extensively researched and proven toxicologically safe, be given priority over TOCP. If a phosphate ester proves most favorable as a heat exchange medium based on other test criteria, consideration could possibly be given to the para and meta isomers of tricresyl phosphate, which do not exhibit the strong toxicological properties of TOCP.

References

1. Weast, R. Handbook of Chemistry and Physics. CRC Press. Chemical Rubber Company. Cleveland, Ohio. 1972.
2. National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. Rockville, Maryland. 1975.
3. American Industrial Hygiene Association. Hygienic Guide Series: Triorthocresyl Phosphate. Detroit, Michigan. 1963.
4. Lefaux, René. Practical Toxicology of Plastics. Iliffe Books Ltd. London, England. 1968.
5. Patty, F.A. Industrial Hygiene and Toxicology: Volume II. Interscience Publishers, John Wiley and Sons Inc. New York. 1967.
6. Smith, M.I., and Lillie, R.D. The Histopathology of Triorthocresyl Phosphate Poisoning. Arch. Neurol. Psychiat. Volume 26. pp. 976-992. 1931.
7. American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values. Third Edition. Cincinnati, Ohio. 1974.
8. Smith, M.I., et al. Further Studies on the Pharmacology of Certain Phenol Esters with Special Reference to the Relation of Chemical Constitution and Physiologic Action. NIH Bulletin. No. 160. pp. 1-53. August, 1932.
9. Smith, M.I., et al. The Pharmacological Action of Certain Phenol Esters with Special Reference to the Etiology of So-Called Ginger Paralysis. U.S. Public Health Reports. Vol. 45, No. 42. pp. 2509-2524. 1930.
10. Hodge, H.C. and Sterner, J.H. The Skin Absorption of Triorthocresyl Phosphate as Shown by Radioactive Phosphorus. J. Pharm. & Exptl. Therap. Vol. 45, pp. 225-234. 1943.
11. Smith, M.K., et al. Pharmacological and Chemical Studies of the Cause of So-Called Ginger Paralysis. U.S. Public Health Reports. Vol. 45, No. 30. pp. 1703-1716. 1930.
12. Smith, V.H. and Spalding, J.M.K. Outbreak of Paralysis in Morocco Due to Ortho-cresyl Phosphate Poisoning. Landet. Vol. 2. pp. 1019-1021. December, 1959.
13. Hamilton, A. and Hardy, H.L. Industrial Toxicology. Publishing Science Group, Inc. Action, Massachusetts. 1974.
14. Plunkett, E.R. Handbook of Industrial Toxicology. Chemical Publishing Company, Inc. New York. 1966.
15. Barnes, J.M. and Denz, F.A. Experimental Demyelination with Organophosphorous Compounds. J. Path. & Bact. Vol. 65. pp. 597-605. 1953.