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MELLON INSTITUTE OF INDUSTRIAL RESEARCH

UNIVERSITY OF PITTSBURGH

SPECIAL REPORT

ON

THE TOXICITY OF THE GLYCOLS AND THEIR DERIVATIVES

58. Single Doses by Skin Absorption of "Carbitol" Acetate.

Carbide & Carbon Chemicals Corp. Industrial Fellowship No. 274-3

Most of the data presented in this report are not satisfactory quantitatively, and the report is issued only for the purposes of record.

Methods

Methods were discussed in report 14 of this series dated June 29, 1938. The only addition is that tin foil was used outside the application for the more volatile materials to reduce loss by vaporization. Samples were the regular commercial grades sold by the chemical company, except in the case of Butyl "Carbitol" Acetate, which was prepared for this work by Fellowship 155 in 1938.

Results

The results are summarized in Table 207 and presented in more detail in Tables 208-212. These results in most cases are only approximations and are listed most briefly below.

Material

LD50

"Carbitol" Acetate

Indeterminate but above 30 gm/kilo

Table 207

Summary of results with single doses by skin absorption
Administered undiluted to mixed guinea pigs on cotton poultices

Material	Dosage in ml/kg.	Pigs Dosed	Mortality
	50	10	50%
	40	10	50
	20	10	50
	10	10	30
	8	10	30
	6	4	0
"Carbitol" Acetate	30	10	40%
	20	4	25
	15	8	12
	10	12	33
	5	10	20
	50	4	100%
	20	10	60
	15	4	0
	30	4*	100%
	20	10	70
	10	10	40
	5	10	60
	3	4*	25
	1	8*	38
	20	4*	100%
	15	10	40
	10	10	60
	5	10	30

*Not in detailed tables

Discussion

These data illustrate the experience of the Fellowship with the skin absorption method when applied to materials of low toxicity. The difficulty is the uncertain contact of large doses with guinea pig skin. It is concluded that this method is unsatisfactory when the LD₅₀ is above 5 grams/kilo. Since the LD₅₀'s of the five materials covered in the present report are all above 5,

they are quantitatively invalid and one can simply say that these five materials have relatively low toxicity when applied to the skin. No further determinations will be made of skin absorption toxicity unless preliminary trials show the ID₅₀ to be less than 5 grams/kilo.

It is felt that this decision is practical, in that it is inconceivable that a human could receive single doses on the skin of 5 grams/kilo which would remain in place long enough for absorption. It certainly appears impossible to make applications of this magnitude to an experimental animal.

Henry F. Smyth, Jr.

Henry F. Smyth, Jr.
SENIOR INDUSTRIAL FELLOW

January 23, 1940-mah

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

UNIVERSITY OF PITTSBURGH

SPECIAL REPORT

SUMMARY OF THE TOXICITY OF THE GLYCOLS AND THEIR DERIVATIVES

64. Single Doses of Glyoxal and Formaldehyde by Mouth and on the Skin

Carbide & Carbon Chemicals Corporation Industrial Fellowship No. 274-3

In single doses by mouth the LD₅₀ of purified Glyoxal for rats is 2 grams/kilo, and for guinea pigs 0.9 gram/kilo. The corresponding figures for Formaldehyde are, respectively, 0.85 gram/kilo and 0.27 gram/kilo.

When these materials are left on the guinea pig skin for four days, both as solutions containing 40 per cent of anhydrous aldehyde, the LD₅₀ of Glyoxal is over 5 grams/kilo, and of Formaldehyde is 0.5 grams/kilo. Glyoxal has no local action, while the local action of Formaldehyde consists of intense irritation and necrosis of the skin.

By mouth, Glyoxal is approximately one-half as toxic in single doses as is Formaldehyde. However, since Glyoxal is probably converted largely to Oxalic Acid in the body, it is probable that its cumulative action would be marked.

In a four-day poulticed application to the guinea pig skin, Glyoxal in 40 per cent solution has no local action, while Formaldehyde has intense local action on the skin. The toxicity of Glyoxal so applied is not more than one-tenth the toxicity of undiluted Formaldehyde.

Where applicable, Glyoxal is much to be preferred to Formaldehyde. It possesses less acute toxicity internally, considerably less skin penetration and markedly less skin injury, in addition to having a negligible vapor pressure and injury by inhalation of vapors should be absent. The cumulative action of Glyoxal is believed to be greater than that of Formaldehyde, but it is probable that in most applications this difference will not be important.

Henry F. Smyth, Jr.


SENIOR INDUSTRIAL FELLOWR: 2-24-40
T: 2-26-40-mah

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

UNIVERSITY OF PITTSBURGH

SPECIAL REPORT

on

THE TOXICITY OF THE GLYCOLS AND THEIR DERIVATIVES64. Single Doses of Glyoxal and Formaldehyde by Mouth and On the Skin

Carbide & Carbon Chemicals Corp.

Industrial Fellowship No. 274-3Samples

The Glyoxal used was a laboratory preparation which had been purified. It was said to contain 90 per cent Glyoxal, with the chief impurity water of crystallization, but traces of Formaldehyde and Formic Acid were present. This was received 9-18-39 from Dr. McNamee of the South Charleston Plant of the Chemical Company. The Formaldehyde was U. S. P. material containing 40 per cent Formaldehyde by weight. All calculations and results are in terms of Anhydrous Glyoxal or Formaldehyde, respectively.

Results

Results are summarized in Table 231, and presented in more detail in Tables 232-236. Since the LD₅₀ of Glyoxal by skin absorption was found to be above 5, it was not determined with accuracy and the detailed animal data are not presented.

Table 231

Glyoxal and Formaldehyde

Summary of Single Doses by Mouth and Skin Absorption

Dosage Grams per Kilo	Rats by Mouth		Guinea pigs by Mouth		Guinea Pigs by Skin	
	Rats Fed	Mortality	Pigs Fed	Mortality	Pigs Dosed	Mortality
Glyoxal						
10					6*	50%
1 ml = 0.10					7*	57
gm by mouth	4	4*	100%			
	3	10	70			
1 ml = 0.40	2	9	56		10*	20
gm on skin	1.5	10	30			
	1.26			6*	100%	
	1.0	4*	0	10	70	
	.775			10	30	
	.63			10	20	
	.39			10*	40	
	.316			6*	16	
LD ₀	1 gm/kg.		0.30 gm/kg.		-	
LD ₅₀	2 "		0.90 "		Over 5 gm/kg.	
LD ₁₀₀	4 "		1.26 "		-	
Formaldehyde						
5					4*	100%
1 ml = 0.02					4*	100
gm by mouth	1.5				6*	100
U.S.P.	1.	6*	100%		10	60
undiluted	.9	10	70			
on skin	.8	10	40			
	.6	10	10			
	.5	6*	0		10	50
	.398			6*	100%	
	.316			9	67	
	.252			10	30	
	.200			10	40	
	.158			6*	0	
LD ₀	0.5 gm/kg.		0.16 gm/kg.		-	
LD ₅₀	0.85 "		0.27 "		0.5 gm/kg.	
LD ₁₀₀	1.0 "		0.40 "		1.5 "	

*Not in detailed tables

Symptoms and Gross Pathology

By mouth as a 10 per cent solution, Glyoxal produces irritation of the digestive tract in the form of congestion and injection of stomach, intestines, and peritoneal wall. Spleen was reddish-orange, liver congested, and kidney extremely pale. During the four-day skin application of a 40 per cent solution of Glyoxal, no local action was found on guinea pigs, but absorption took place because the internal organs had the same gross appearance as when this material was administered by mouth, including the congestion of the peritoneal contents.

When Formaldehyde was administered by mouth as a 2 percent solution, prostration and convulsions rapidly followed large doses and death was rapid. There was intense irritation of the entire digestive tract, much more severe than with 10 per cent Glyoxal solution, and the intestines were opaque suggesting protein coagulation. Liver, kidney and spleen were pale. When applied to guinea pig skin as a 40 per cent solution (undiluted U.S.P. Formaldehyde), intense local irritation, necrosis of several layers of skin and gelatinous exudate resulted. This skin application produced intense peritoneal congestion.

Discussion

By mouth Glyoxal is approximately one-half as toxic in single doses as is Formaldehyde. However, since Glyoxal is probably converted largely to Oxalic Acid in the body, it is probable that its cumulative action would be marked.

In a four-day poulticed application to the guinea pig skin, Glyoxal in 40 per cent solution has no local action, while Formaldehyde has intense local action on the skin. The toxicity of Glyoxal so applied is not more than one-tenth the toxicity of undiluted Formaldehyde.

Where applicable, Glyoxal is much to be preferred to Formaldehyde. It possesses less acute toxicity internally, considerably less skin penetration, and markedly less skin injury, in addition to having a negligible vapor pressure, and injury by inhalation of vapors should be absent. The cumulative action of Glyoxal is believed to be greater than that of Formaldehyde, but it is probable that in most applications this difference will not be important.

Henry F. Smyth, Jr.

Henry F. Smyth, Jr.

 SENIOR INDUSTRIAL FELLOW

February 26, 1940-mah

Table 232

Strychnine

Single Doses to Male Rats by Mouth

Fed by stomach tube as solution in water, 1 ml = 0.10 gm. = 0.125 gm. sample

Rat No.	Date Dosed	Grams Ft.	Weight Change in 14 Days	Dosage; Grams per Kilo	Dose in Grams	Dose in ml. of Solution	Days to Death
5489	9-27-39	92	-	3	.276	2.8	2
5490	"	87	-	3	.26	2.6	2
5491	"	68	-	3	.204	2.0	1
5492	"	84	-	3	.252	2.5	1
5696	10-25	106	-	3	.318	3.2	2
5698	"	102	-	3	.306	3.1	1
5699	"	102	-	3	.306	3.1	1
5695	"	102	- 7	3	.306	3.1	1
5697	"	76	+ 36	3	.288	2.9	-
5700	"	97	0	3	.291	2.9	-
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5402	9-21	102	-	2	.20	2.0	1
5403	"	94	-	2	.19	1.9	1
5405	"	84	-	2	.17	1.7	2
5480	10-5	102	-	2	.22	2.2	1
5483	"	96	-	2	.19	1.9	1
5479	"	90	+ 39	2	.13	1.3	-
5481	"	85	+ 23	2	.17	1.7	-
5482	"	96	- 24	2	.19	1.9	-
5484	"	90	+ 35	2	.18	1.8	-
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5521	10-5	88	-	1.5	.13	1.3	11
5522	"	80	-	1.5	.12	1.2	2
5702	10-25	80	-	1.5	.12	1.2	6
5517	10-5	82	+ 20	1.5	.12	1.2	-
5518	"	80	+ 28	1.5	.12	1.2	-
5519	"	95	+ 37	1.5	.14	1.4	-
5520	"	115	+ 39	1.5	.17	1.7	-
5701	10-25	85	+ 20	1.5	.128	1.3	-
5703	"	89	+ 45	1.5	.134	1.3	-
5704	"	88	+ 53	1.5	.13	1.3	-

Title 271

Muskrat

Single Doses to Mixed Guinea Pigs

Fed by stomach tube as solution in water
 1 ml = 0.10 gm. = 0.125 gm. sample

Fig. No.	Sex	Date Dosed	Grams Wt.	Weight Change in 14 Days	Dosage Grams per Kilo	Dose in Grams	Dose in ml. of Dispersion	Days to Death
5775	M	12-8-39	235	-	1.0	0.24	2.4	3
5777	M	"	174	-	1.0	0.17	1.7	1
6079	M	12-19-39	220	-	1.0	0.22	2.2	1
5754	F	12-1-39	216	-	1.0	0.21	2.1	6
5735	F	"	213	-	1.0	0.21	2.1	1
5776	F	12-8-39	198	-	1.0	0.20	2.0	1
6097	F	12-19-39	205	-	1.0	0.20	2.0	1
5774	M	12-8-39	263	- 2	1.0	0.26	2.6	2
6098	M	12-19-39	237	+ 21	1.0	0.24	2.4	-
6110	F	12-19-39	223	+ 17	1.0	0.22	2.2	-
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5779	M	12-8-39	186	-	.775	0.15	1.5	1
6223	M	1-5-40	246	-	.775	0.20	2.0	4
6103	F	12-19-39	291	-	.775	0.23	2.3	1
5780	M	12-8-39	292	- 7	.775	0.23	2.3	-
5781	M	"	290	- 20	.775	0.22	2.2	-
6100	M	12-19-39	226	+ 39	.775	0.18	1.8	-
6101	M	"	235	+ 23	.775	0.19	1.9	-
6102	M	"	225	- 49	.775	0.18	1.8	-
6222	M	1-5-40	252	- 38	.775	0.20	2.0	-
5778	F	12-8-39	253	- 11	.775	0.20	2.0	-
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5732	M	12-1-39	230	-	.63	0.16	1.6	3
6299	F	1-9-40	165	-	.63	0.10	1.0	4
6105	M	12-19-39	206	+ 38	.63	0.13	1.3	-
6107	M	"	202	+ 46	.63	0.13	1.3	-
6221	M	1-5-40	269	+ 42	.63	0.17	1.7	-
5733	F	12-1-39	220	+ 18	.63	0.14	1.4	-
6104	F	12-19-39	241	+ 44	.63	0.15	1.5	-
6106	F	"	197	+ 6	.63	0.12	1.2	-
6220	F	1-5-40	240	- 13	.63	0.15	1.5	-
6298	F	1-9-40	169	+ 93	.63	0.11	1.1	-

Table 234

Formaldehyde

Single Doses to Male Rats by Mouth:

Fed by stomach tube as dilution in water

1 ml = 0.02 gm. anhydrous formaldehyde, or 0.05 gm. U.S.P. 40% formaldehyde

Ext. No.	Date Recd.	Gram Wt.	Weight Change in 14 Days	Dosage; Grams per Kilo	Dose in Grams	Dose in ml. of Dilution	Days to Death
6158	12-28-39	107	-	0.9	.096	4.8	1
6159	"	125	-	0.9	.113	5.6	1
6160	"	89	-	0.9	.080	4.0	1
6161	"	113	-	0.9	.102	5.1	1
6162	"	75	-	0.9	.068	3.4	1
6166	"	107	-	0.9	.096	4.8	1
6167	"	99	-	0.9	.089	4.4	1
6162	"	119	+ 38	0.9	.107	5.4	-
6163	"	115	+ 55	0.9	.102	5.2	-
6165	"	89	+ 32	0.9	.080	4.0	-
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5920	11-29	90	-	0.8	.072	3.6	1
6015	12-7	86	-	0.8	.069	3.4	1
6-16	"	95	-	0.8	.076	3.8	1
6087	11-21	91	-	0.8	.072	3.6	1
5952	11-29	104	+ 42	0.8	.083	4.1	-
5953	11-29	98	+ 55	0.8	.078	3.9	-
5921	11-29	92	+ 26	0.8	.074	3.7	-
6014	12-7	82	+ 44	0.8	.066	3.3	-
6017	"	93	+ 29	0.8	.074	3.7	-
6088	12-12	77	+ 95	0.8	.062	3.1	-
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6081	12-12	73	-	0.6	.044	2.2	4
6018	12-7	94	+ 38	0.6	.056	2.8	-
6-19	"	99	+ 39	0.6	.059	3.0	-
6020	"	90	+ 16	0.6	.054	2.7	-
6021	"	90	+ 22	0.6	.054	2.7	-
6082	12-12	79	+ 53	0.6	.047	2.4	-
6083	"	97	+ 49	0.6	.058	2.9	-
6084	"	77	+ 19	0.6	.046	2.3	-
6085	"	103	+ 48	0.6	.062	3.1	-
6157	12-28	127	+ 51	0.6	.476	3.8	-

Table 235

Formaldehyde

Single Doses to Mixed Guinea Pigs by Mouth
 Fed by stomach tube as dilution in water, 1 ml = 0.02 gm.
 Anhydrous Formaldehyde, or 0.05 gm. U.S.P. 40% Formaldehyde

Pig No.	Sex	Date Dosed	Grams Wt.	Weight Change in 14 Days	Dosage; Grams per Kilo	Dose in Grams	Dose in ml. of Dilution	Days to Death
5982	H	12-8-39	230	-	.316	.073	3.6	1
5984	H	"	250	-	.316	.079	4.0	1
5985	H	"	226	-	.316	.072	3.6	3
6161	F	12-20	239	-	.316	.076	3.8	1
6162	F	"	235	-	.316	.074	3.7	1
6163	F	"	210	-	.316	.066	3.3	1
6164	H	"	267	+ 14	.316	.084	4.2	-
6219	H	1-5-40	250	- 5	.316	.079	4.0	-
5983	F	12-8-39	238	- 31	.316	.082	4.1	-
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5946	H	12-1-39	300	-	.252	.076	3.8	3
6250	H	1-9-40	238	-	.252	.060	3.0	1
6248	F	"	212	-	.252	.051	2.6	1
5947	H	12-1-39	194	+ 3	.252	.049	2.4	-
6249	H	1-9-40	194	- 9	.252	.049	2.4	-
6157	F	12-20-30	251	+ 49	.252	.063	3.2	-
6158	F	"	242	- 37	.252	.062	3.0	-
6159	F	"	219	- 38	.252	.055	2.8	-
6160	F	"	247	- 47	.252	.062	3.1	-
6247	F	1-9-40	188	+ 87	.252	.047	2.4	-
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6112	H	12-20-39	248	-	.200	.050	2.5	0
6214	H	1-5-40	242	-	.200	.048	2.4	14
6216	H	"	242	-	.200	.048	2.4	1
6215	F	"	273	-	.200	.055	2.8	5
6111	H	12-20-39	200	+ 69	.200	.040	2.0	-
6113	F	"	215	+ 79	.200	.040	2.0	-
6156	F	"	219	- 20	.200	.044	2.2	-
6212	F	1-5-40	260	- 56	.200	.050	2.5	-
6213	F	"	237	+ 24	.200	.047	2.4	-
6217	F	"	248	+ 1	.200	.050	2.5	-

Table 236

Formaldehyde

Single Doses to Mixed Guinea Pigs by Skin Absorption
Administered on cotton poultices with tin foil protection,
as 40% solution (U.S.P. Formaldehyde) but calculated as anhydrous material

Pig No.	Sex	Date Clipped	Date Applied	Date Poultice Removed	Grams Wt.	Weight Change in 14 Days	Dosage; Grams per Kilo	Dose in Grams	Dose in Ml.	Days to Death
5673	M	9-21-39	9-22	9-26	212	-	1	.24	.60	5
5718	M	10-3	10-4	10-9	222	-	1	.22	.55	9
5674	F	9-21	9-22	9-26	236	-	1	.24	.60	6
5675	F	"	"	"	255	-	1	.255	.65	8
5719	F	10-3	10-4	-	213	-	1	.21	.55	5
5722	F	"	"	-	190	-	1	.19	.47	2
5676	M	9-21	9-22	9-26	230	+ 27	1	.23	.60	-
5720	F	10-3	10-4	10-9	169	+ 11	1	.169	.42	-
5721	F	"	"	"	202	+ 28	1	.202	.50	-
5723	F	"	"	"	246	- 2	1	.246	.62	-
5708	F	10-3	10-4	10-9	186	-	0.5	.092	.23	13
5709	F	"	"	"	194	-	0.5	.097	.24	13
5712	F	"	"	"	184	-	0.5	.092	.23	4
5716	F	"	"	"	226	-	0.5	.113	.28	9
5717	F	"	"	"	238	-	0.5	.119	.30	9
5710	M	"	"	"	233	+ 32	0.5	.116	.29	-
5714	M	"	"	"	207	+ 5	0.5	.104	.26	-
5715	M	"	"	"	228	+ 27	0.5	.114	.28	-
5711	F	"	"	"	230	+ 3	0.5	.115	.29	-
5713	F	"	"	"	191	- 3	0.5	.095	.24	-

K: 4-27-40
JRS

MELLON INSTITUTE OF INDUSTRIAL RESEARCH
University of Pittsburgh

PROGRESS REPORT for the Month ended April 30, 1940

Carbide & Carbon Chemicals Corporation Industrial Fellowship No. 274-3

Confidential

R: 3-29-48

Report No. 11-52

KH6 3/3/48

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

UNIVERSITY OF PITTSBURGH

PROGRESS REPORT for the month ended March 31, 1948

Carbide and Carbon Chemicals Corporation

Industrial Fellowship No. 274-11

Subjects under)	Work in Progress	Single Oral Dose to Rabbits
which report is)	Special Reports	Single Skin Absorption
to be indexed)	Primary Irritation	Single Oral Dose to Rats
	Miscellaneous Toxicity Data	
	Single Oral Dose to Rats	
		Trips

Work in Progress

The following projects have been started and are being pushed as rapidly as circumstances permit. Those marked with an asterisk (*) are finished except for completion of tissue study.

<u>C.P.I. No.</u>	<u>Grade</u>	<u>Score</u>
	B	7
	B	7
	B	8
	C	12
	D	17
	E	20 + (necrosis)
	D	16

A sample of ethyl ' which had been stored in drums at Charleston since the Fall of 1946 was tested. It fell in Grade B with a score of 8 and was judged suitable for sale.

Miscellaneous Toxicity Data

The following results on materials in our standby list will not appear in special reports. Our rat specifications are somewhat relaxed for standby materials and some of these data, where indicated, were obtained on 90 to 120 gram female rats.

Single Oral Dose to Rats, LD₅₀ in gm./kg.

→ Acetaldehyde 1.93 (1.64 to 2.24)

* This compound was verbally reported to us as responsible for the toxicity of as an intermediate in its metabolism. We find its toxicity identical with that of and hence doubt the report.

Single Oral dose to rabbits, LD₅₀ in gm./kg.

8.80 (8.42 to 9.19)

Single Skin Absorption by rabbits, LD₅₀ in ml./kg.

0.38 (0.27 to 0.52)

L'16/26/51

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

UNIVERSITY OF PITTSBURGH

SPECIAL REPORT

33

Range Finding Tests on 2-Ethylhexaldehyde

Series of Procedures

Carbide & Carbon Chem. Div. of U.C.C. Industrial Fellowship 274-14Summary

2-Ethylhexaldehyde is a moderately toxic compound for rats in single oral doses. The R.F. LD50 for males is 3.73 (2.43 to 5.74) gm./kg. and the advanced LD50 for females 4.08 (3.67 to 4.54) gm./kg. when fed as 20% dispersions. Oral toxicity is comparable to 2-ethylbutyraldehyde and about 1/2 that of acetaldehyde.

By skin penetration the R.F. LD50 for rabbits subjected to 24 hour contact with the undiluted product under "Vinylite" sheeting, is 5.04 (3.40 to 7.46) ml./kg.

Inhalation of saturated vapor at room temperature for 1 hour caused the immediate death of 2 of 6 female rats by virtue of lung damage. The remainder survived and gained weight during the observation period. Further work indicates that the vapors of this compound constitute a moderate hazard upon inhalation.

Erythema comparable to that caused by xylene is produced on the skin of the rabbit belly in the vesicant test.

Rabbit eyes vary widely in their response to undiluted 2-ethylhexaldehyde. Some will have severe damage and others will be normal 24 hours after the application. On the basis of the rabbit work the compound falls in Grade 2 of the 10 Grade rating system or comparable in damage created to "Carbitol". On the basis of painfulness and effect on the conjunctiva the aldehyde is many times worse than "Carbitol".

Sample

The 2-ethylhexaldehyde used in these studies was received from South Charleston on 11-20-50 under "Passed" #71291. Dr. Nais requested complete Range Finding Tests.

Single Oral Doses

The R.F. LD50 for male albino rats fed a 20% dispersion in 1% "Tergitol" 7 is 3.73 (2.43 to 5.74) gm./kg. and the Advanced LD50 for females of the same weight range is 4.08 (3.67 to 4.54) gm./kg.

Thompson's method of estimating the median-effective dose (LD50) was applied to the 14-day mortality data. Sherman strain, non-fasted rats, 5 to 6 weeks of age weighing 90 to 120 grams were fed the compound in single doses by stomach tube. This stock was reared in our own colony on Rockland rat diet (complete).

Symptoms which included sluggishness, roughening of the coat, prostration and narcosis followed the administration of dosage levels within and above the range quoted for the LD50's.

Autopsy findings on rats that had succumbed as the result of an oral dose included lung congestion or hemorrhage, congestion of the liver and kidneys, and congestion and opaqueness of the gastrointestinal tract. The latter damage was caused by the direct burning action of the aldehyde.

This compound is comparable in acute oral toxicity to butyraldehyde LD50 5.9 gm./kg. and to 2-ethylbutyraldehyde LD50 3.98 gm./kg. but it is about 1/2 as toxic as acetaldehyde LD50 1.93 gm./kg.

Skin Penetration

The R. F. LD50 by this route for rabbits is 5.04 (3.40 to 7.46) ml./kg. for the undiluted compound.

Male albino New Zealand strain rabbits, 3 to 5 months of age averaging 2.5 kg. in weight were immobilized during a 24 hour contact period with the chemical. Thereafter the "Vinylite" sheeting, used to retain the fluid in contact with the clipped skin of the trunk, was removed and the rabbits were caged during the remainder of the 14 day observation period. Locally purchased rabbits maintained by us on Rockland rabbit ration were used.

The aldehyde caused erythema and later desquamation of the skin. Autopsy of those that died revealed congested lungs, pale or mottled livers and kidneys and congested intestines.

Inhalation

Saturated vapor was produced at room temperature by passing air at 2.5 liters/min. through a fritted glass disc immersed in 50 ml. of the chemical in a gas washing bottle. Two of six young mature female rats died during a 1 hour exposure but the remaining 4 survived and gained weight during the subsequent 14 day observation period. The temperature in the gas washing bottle rose to 50° C. during the aeration of the aldehyde because of polymerization. It is quite probable that a fog was produced in addition to saturated vapor and that the figure for saturation at 20° C. (2360 ppm.) was exceeded by a considerable amount. The hazard created by saturated vapor of this compound is definite.

Based upon empirical calculation a metered concentration of 8000 ppm. was established and rats were exposed for 4 hours. All of 6 young female rats succumbed in this exposure with extreme lung damage, congestion and hemorrhage. The vapor condensed on the walls of the chambers and it is certain that saturation was exceeded. However, the figure for saturation at room temperature (25° C.) is undoubtedly less than 8000 ppm.

However, if we grant that 4000 ppm. is attainable, then we have fair agreement with the results of a 4 hour exposure to this reported concentration and our saturated vapor exposure data. Only 1 of 6 rats succumbed as a result of a 4 hour exposure to a metered 4000 ppm. while 2 of 6 died in 1 hour in a concentration which exceeded saturation by virtue of the presence of a fog.

2-Ethylhexaldehyde would therefore be characterized as a compound of moderate hazard by the respiratory route when inhaled for periods of 4 hours or less at concentrations approaching saturation at 20° C. (2360 ppm.).

Skin Irritation

The application of 0.01 ml. amounts of the undiluted compound in the rabbit belly vesicant test resulted in moderate or marked erythema being produced on 5 different rabbits 24 hours after the application. This placed 2-ethylhexaldehyde in Grade 5 of the 10 Grade rating system along with xylene, mono and diethanolamine.

Eye Burns

There is wide variation in the response of individual rabbit eyes to the instillation of undiluted 2-ethylhexaldehyde. The first 5 rabbit eyes that were dosed with 0.5 ml. amounts showed slight or no injury. This seemed unlikely in view of our results with butyraldehyde which falls in Grade 8 of our 10 Grade rating system. Five more eyes were dosed with 0.5 ml. amounts and all were severely burned or they showed internal congestion along

with pus formation and swelling of the eyelids. Faced with these conflicting results the third trial was attempted by the writer himself.

The results of third trial proved that some rabbits are badly burned and others are practically normal 24 hours after the introduction of 0.5 ml. of the undiluted compound. On this basis the compound falls in Grade 2 of the 10 Grade rating system.

It is beyond our ability to predict exactly the response of the human eye but it is certain from observation of animals that 2-ethylhexaldehyde will be most painful when introduced into the eye, that the lids will be swollen, pus will most likely be formed. Whether or not internal congestion and severe corneal damage will result we do not know.


SENIOR INDUSTRIAL FELLOW

Charles P. Carpenter

Typed January 22, 1951 -src

Table 14-44

2-ETHYLHEXALDEHYDE

Single Doses to Male Albino Rats by Mouth

Fed by Stomach Tube as a Dispersion in 1% "Tg" 7, 1 ml. = 0.20 gm.

Rat No.	Date Dosed	Grams Wt.	Weight Change in 14 Days	Dosage; Grams per Kilo	Dose in Grams	Dose in ml. of Dispersion	Days to Death
10899	11-21-50	94	-	7.95	0.747	3.7	1
10952	"	92	-	7.95	0.731	3.7	1
10950	"	123	-	7.95	0.938	3.7	1
10933	"	97	-	7.95	0.779	3.9	1
10863	"	106	-	7.95	0.843	4.2	1
10962	11-21-50	119	-	3.98	0.474	2.4	2
10924	"	96	-	3.98	0.382	1.9	1
10920	"	100	-	3.98	0.398	2.0	1
10925	"	106	-	3.98	0.422	2.1	1
10921	"	114	-	3.98	0.454	2.3	1
10414	11-21-50	100	-	2.00	0.200	1.00	11
10443	"	100	-	2.00	0.212	1.10	4
10476	"	92	+ 56	2.00	0.184	0.92	-
10446	"	104	+ 52	2.00	0.208	1.00	-
10444	"	100	+ 37	2.00	0.200	1.00	-
11166	12-12-50	114	-	1.00	0.111	0.57	3
10928	11-29-50	104	+ 44	1.00	0.104	0.52	-
10864	"	101	+ 7	1.00	0.101	0.50	-
10664	"	105	+ 37	1.00	0.105	0.52	-
10635	"	114	+ 35	1.00	0.114	0.57	-

For calculation of the R.F. LD50 by the method of Thompson, 100% survival at 0.5 gm./kg. was assumed for 5 rats.

Table 14-45

2-ETHYLHEXALDEHYDE

Single Doses to Rabbits by Skin PenetrationAdministered undiluted under "Vinylite" dam for 24 hours

Rabbit No.	Date Clipped	Date Applied	Gm. Wt.	Weight Change in 14 Days	Dosage; Ml. per Kilo	Dos in Ml.	Days to Death
7692	11-24-50	11-24-50	2370	-	10.0	23.7	1
7693	"	"	2528	-	10.0	25.3	1
7671	12-4-50	12-4-50	2532	-	10.0	25.3	1
7672	"	"	2473	-	10.0	24.8	1
7682	11-21-50	11-21-50	2402	-	5.0	12.0	3
7704	12-4-50	12-4-50	2940	-	5.0	14.7	1
7695	"	"	2712	+ 56	5.0	13.6	-
1408	12-5-50	12-5-50	2864	- 232	5.0	14.3	-
7620	11-30-50	11-30-50	2600	+ 128	2.52	6.6	-
7621	"	"	2554	- 28	2.52	6.4	-
7701	"	"	2884	- 132	2.52	7.3	-
7702	"	"	2662	- 372	2.52	6.7	-

For calculation of the R.F. LD50 by the method of Thompson 4 rabbits were assumed to survive at a dosage level of 1.26 ml./kg.

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Report 14-24

R: 2-16-51

LHO 2/2/51

MELLON INSTITUTE OF INDUSTRIAL RESEARCH
UNIVERSITY OF PITTSBURGH
SPECIAL REPORT

on

Range Finding Tests on Propionaldehyde

Tables of Protocols Attached.

Carbide and Carbon Chem Div., U.C.C. Industrial Fellowship No. 274-14

SUMMARY

Propionaldehyde is a compound of moderate acute oral toxicity for rats with a R.F. LD₅₀ of 1.41 (0.96 to 2.08) gm./kg. It is slightly less toxic than formaldehyde by this route.

The R.F. LD₅₀ for rabbits by skin penetration is 5.0 (3.4 to 7.5) ml./kg. for the undiluted compound and by this route it is only 1/50 as toxic as formaldehyde in 40% solution.

Substantially saturated vapor at room temperature is dangerous for the reason that approximately 300,000 ppm. may be achieved - which concentration is rapidly lethal if inhaled.

Rats tolerated a concentration of 4000 ppm. for 4 hours without ill effect, indicating that the actual toxicity of the vapors is not great.

Propionaldehyde evaporates so rapidly from intact skin that it causes slight irritation in uncovered applications to rabbits. It falls in Grade 5 of the 10-grade eye burn rating system together with acetone and triethanolamine.

Sample

To aid in the correct labelling of propionaldehyde, Dr. Nale requested toxicity data on the compound. On 12-11-50 a 16-oz. quantity was procured from South Charleston identified by number D-1684-132.

Single Oral Doses

The R.F. LD₅₀ for male albino rats fed a 20% dispersion in 1.0% "Tergitol" 7 is 1.41 (0.96 to 2.08) gm./kg.

Thompson's method of calculating the median-effective dose (LD₅₀) was applied to the 14-day mortality data. Sherman strain, non-fasted rats, 5 to 6 weeks of age and weighing 90 to 120 grams were fed the compound by stomach tube.

These rats were reared in our own colony and maintained exclusively on Arcady Milling Co. Rockland rat diet (complete). Symptoms of distress were more manifest as the dosage level increased. Roughening of the coat and prostration were noted at 2 and 4 gm./kg. while convulsions and death within 2 minutes after dosing followed an 8 gm./kg. dosage.

Autopsy of victims revealed a cooked appearance of the gastrointestinal tract, congestion of the peritoneal wall and a distinct odor of onions emanated from the carcasses.

Oral LD₅₀'s for comparison are as follows: butyraldehyde 5.9 gm./kg., ethyl butyraldehyde 3.98, ethylhexaldehyde 4.1 and formaldehyde 0.795 gm./kg.

Skin Penetration

By skin penetration of the undiluted compound the R.F. LD₅₀ is 5.0 (3.4 to 7.5) ml./kg.

Propionaldehyde was retained for 24 hours under impervious "Vinylite" sheeting which encircled the clipped trunk of male albino New Zealand rabbits averaging 2.5 kg. in weight. Mortality data were based upon a total observation period of 14 days. The rabbits used in these tests were purchased from a dealer and were maintained on Rockland rabbit ration throughout the course of this test.

Autopsy of those succumbing as a result of the toxicity of propionaldehyde revealed erythema, desquamation, and some tanning action on the skin, pale and mottled livers and kidneys and lung congestion.

Propionaldehyde does not penetrate skin to anywhere near the extent of 40% formaldehyde. The latter has a R.F. LD₅₀ of 0.11 gm./kg. by this route.

Inhalation

Substantially saturated vapor generated at room temperature by passing air at 2.5 l./min. through a fritted glass disc immersed in 50 ml. of the compound in a gas washing bottle killed 6 of 6 rats in 10 minutes, 2 of 6 in a 5-minute exposure and 0 of 5 in a 2-minute exposure. Saturated vapor at room temperature is a serious hazard and such exposures must be avoided. The compound causes extreme lung irritation as evidenced by the finding of edema, congestion and hemorrhage in rats succumbing to this type of exposure.

A concentration of 16,000 ppm. killed 6 of 6 mature male rats in 2-1/4 hours, 8000 ppm. killed 5 of 6 in 4 hours and 4000 was not lethal in 4 hours. Autopsy findings were similar to those described above.

It is obvious from the above that the extremely high vapor pressure (225 mm. at 20° C.) of this compound is responsible for its being a serious hazard, for saturation at room temperature would be on the order of 300,000 ppm. Its actual toxicity would be termed moderate on the basis of the rat results at known concentrations.

Irritation

Only 1 of 5 rabbits reacted as a result of the application of 0.01 ml. amounts of undiluted propionaldehyde to the intact skin of the clipped belly. This places the compound in Grade 2 for this one response on an extremely reactive rabbit was marked erythema. This degree of irritation is comparable to that produced by methyl ethyl ketone.

Rabbit eyes were severely injured by 0.02 ml. amounts of the undiluted chemical and 0.005 ml. doses cause moderate damage. These results place propionaldehyde in Grade 5 of the 10-grade eye burn rating system or comparable in effect to acetone and triethanolamine.


SENIOR INDUSTRIAL FELLOW

Charles F. Carpenter

Typed: February 17, 1951 - mek

Table 14-80

Propionaldehyde

Single Doses to Male Albino Rats by Mouth

Fed by Stomach Tube as a Dispersion in 1% "Teratol" 7, 1 ml. = 0.20 gm.

Rat Number	1950 Date Dosed	Grams Wt.	Weight Change in 14 Days	Dosage; Grams per Kilo	Dose in Grams	Dose in ml. of Dispersion	Days to Death
11802	12-19	116	-	3.98	0.462	2.3	1
11799	"	102	-	3.98	0.406	2.0	1
12086	"	92	-	3.98	0.366	1.8	1
12085	"	100	-	3.98	0.398	2.0	1
12082	"	112	-	3.98	0.446	2.2	1
12088	12-19	106	-	2.00	0.212	1.1	1
12109	"	114	-	2.00	0.228	1.1	14
12106	"	102	-	2.00	0.204	1.0	1
11522	"	108	-	2.00	0.216	1.1	1
11527	"	112	+ 26	2.00	0.224	1.1	-
11827	12-12	108	-	1.00	0.108	0.54	1
11842	"	100	+ 65	1.00	0.100	0.50	-
11791	"	112	+ 78	1.00	0.112	0.56	-
11789	"	100	+ 92	1.00	0.100	0.50	-
11771	"	90	+ 67	1.00	0.090	0.45	-
11907	12-19	112	+ 48	0.500	0.056	0.28	-
11350	"	102	+ 54	0.500	0.051	0.26	-
11781	"	116	+ 56	0.500	0.058	0.29	-
11405	"	116	+ 60	0.500	0.058	0.29	-
12104	"	114	+ 56	0.500	0.057	0.29	-

Table 14-81

Propionaldehyde

Single Doses to Male Albino Rabbits by Skin Penetration
Administered Undiluted under "Vinylite" Dam for 24 Hours

Rabbit Number	1951 Date Clipped	1951 Date Applied	Grams Wt.	Weight Change in 14 Days	Dosage; Ml. per Kilo	Dose in Ml.	Days to Death
7932	2-8	2-8	2688	-	10.0	26.9	1
7933	"	"	3060	-	10.0	30.6	1
7942	"	"	3182	-	10.0	31.8	1
7280	1-17	1-17	4092	-	5.0	20.5	7
7734	"	"	3640	-	5.0	18.2	1
7714	"	"	2600	- 212	5.0	13.0	-
7743	"	"	2943	+ 263	5.0	14.7	-
7632	12-18	12-18	2718	+ 162	2.52	6.8	-
7710	"	"	2654	+ 252	2.52	6.7	-
7746	1-17	1-17	2966	+ 112	2.52	7.5	-
7778	"	"	2706	+ 56	2.52	6.8	-

For calculation of the R.F. LD₅₀ by Thompson's method, a mortality of 4 of 4 rabbits was assumed for a dosage level of 10 ml./kg. and 0/4 at 1.26 ml./kg.

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Report 15-55

Rs 6-30-52

E. W. D. 7-8-52

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

UNIVERSITY OF PITTSBURGH

SPECIAL REPORT

01

Range Finding Tests on Isobutyraldehyde

Tables of Protocols Attached

Carbide and Carbon Chem. Co., U.C.C. Industrial Fellowship No. 274-15

Summary

Isobutyraldehyde is a moderately toxic compound with an oral LD₅₀ for rats of 3.7 (2.7 to 5.2) gm./kg. This is slightly more toxic than n-butyraldehyde which has an LD₅₀ under similar test conditions of 5.9 gm./kg.

By skin penetration for rabbits the estimated LD₅₀ is 7.1 ml./kg. for isobutyraldehyde while that for n-butyraldehyde is 3.6 ml./kg.

Substantially saturated vapor generated at room temperature is lethal to rats in 30 minutes and not in 15 minutes. A concentration of 16,000 ppm is likewise lethal in 4 hours while 8,000 ppm. is not. Vapor toxicity is similar to that of n-butyraldehyde. Although the vapors are not particularly toxic the high vapor pressure will allow relatively enormous and lethal concentrations to be formed at room temperature.

Rapid evaporation from the skin surface prevented any irritation to the clipped skin of the rabbit belly when applied in 0.01 ml. amounts.

Rabbit eyes were injured with isobutyraldehyde to about the same degree as with acetone.

Sample

Two 8-ounce samples of isobutyraldehyde were received 4-3-52 from S. Charleston for toxicity evaluation. The Works Lab Passed # was S 61640.

Single Oral Doses

The LD₅₀ for female rats fed a 20% dispersion in 1% aqueous "Tergitol" 7 is 3.7 (2.7 to 5.2) gm./kg.

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Page 2.

Carworth Wistar, non-fasted rats, 5 to 6 weeks of age and 90-120 grams in weight were dosed at levels differing by a factor of 2.0 in a geometric series. The rats were reared in our own colony and maintained from time of weaning on Rockland rat diet (complete). Thompson's method of calculating the median-effective dose (LD_{50}) was applied to the 14-day mortality data.

This dispersion caused severe gastrointestinal tract necrosis. The liver, spleen and kidney also were necrosed where they contacted the stomach wall. Lungs were markedly congested or hemorrhagic.

Isobutyraldehyde is slightly more toxic in single oral dose for rats than is n-butyraldehyde which has an LD_{50} for female rats, dosed similarly, of 5.9 gm./kg.

Skin Penetration

The most probable LD_{50} for rabbits is 7.1 ml./kg. based upon the death of 4 rabbits dosed at 10 ml./kg. and the survival of 2 dosed at 5 ml./kg.

Male albino New Zealand strain rabbits, 3 to 5 months of age and averaging 2.5 kg. in weight were immobilized during the 24-hour skin contact period. Thereafter, the "Vinylite" sheeting used to retain the dose in contact with the clipped skin of the trunk was removed and the animals were caged for the remainder of the 14-day observation period. The rabbits were procured locally and maintained on Rockland rabbit ration. Thompson's method of calculating the LD_{50} was used assuming that 20 ml./kg. would be lethal and that 5 and 2.52 ml./kg. would allow survival of 4 rabbits on each level.

Erythema, edema and necrosis were produced on the skin, and the lungs of victims were congested or hemorrhagic. N-butyraldehyde has an LD_{50} of 3.6 ml./kg. in this test.

Inhalation

Substantially saturated vapor, generated at room temperature by passing air at 2.5 liters/minute through a fritted glass disc immersed in 50 ml. of the compound caused the death of 4 of 6 rats exposed for 30 minutes and 0 of 6 exposed 15 minutes. N-butyraldehyde killed 1 of 6 in 10 min. and 6 of 6 in 20 minutes.

Upon inhalation for 4-hour periods, a concentration of 16,000 ppm. killed 6 of 6 rats and 8000 ppm. 1 of 6. Previous results with the n-butyraldehyde were identical.

Irritation

The application of 0.01 ml. amounts of undiluted isobutyraldehyde to the clipped skin of the rabbit belly produced no reactions probably because it rapidly evaporates.

A 0.02 ml. amount of the undiluted chemical caused severe damage to the cornea of the rabbit eyes while 0.005 ml. amounts caused moderate injury. These results place it in Grade 5 of the 10 grade rating system in company with acetone.


SENIOR INDUSTRIAL FELLOW

Charles P. Carpenter

Typed: July 1, 1952 - nek

Table 15-167

Isobutyraldehyde

Single Doses to Female Albino Rats by Mouth

Fed by Stomach Tube as a Dispersion in 1% "Tg" 7, 1 ml. = 0.20 gm.

Rat Number	1952 Date Dosed	Grams Wt.	Weight Change in 14 Days	Dosage; Grams per Kilo	Dose in Grams	Dose in ml. of Dispersion	Days to Death
33221	4-10	102	-	7.95	0.811	4.1	0
33248	"	95	-	7.95	0.755	3.8	0
33242	"	103	-	7.95	0.819	4.1	0
33251	"	101	-	7.95	0.803	4.0	0
32675	"	100	-	7.95	0.795	4.0	0
32739	4-10	97	-	3.98	0.386	1.9	0
32724	"	99	-	3.98	0.394	2.0	0
32741	"	95	-	3.98	0.374	1.9	-
32723	"	106	+ 24	3.98	0.422	2.1	-
32729	"	99	+ 35	3.98	0.394	2.0	-
33169	4-10	110	- 8	2.0	0.220	1.1	-
33265	"	107	+ 17	2.0	0.214	1.1	-
33206	"	95	+ 33	2.0	0.190	0.95	-
33247	"	98	+ 28	2.0	0.196	0.98	-
33192	"	100	+ 42	2.0	0.200	1.00	-

LD₅₀ = 3.73 (2.69 to 5.21) gm./kg.For calculation of the LD₅₀ by Thompson's method 100% survival was assumed for 6 rats at 1.0 gm./kg.

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Report 16-98

Rs 11-12-53

LHG 11/13/53

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

UNIVERSITY OF PITTSBURGH

SPECIAL REPORT

on

Range Finding Tests on Tetrahydrobenzaldehyde

Carbide and Carbon Chem. Co., U.C.C. Industrial Fellowship No. 274-16

Summary

This compound is moderately toxic in single oral doses. The LD₅₀ for rats fed a 10% dilution in corn oil is 2.5 (2.2 to 2.7) gm./kg. For comparison trimethyl tetrahydrobenzaldehyde has an LD₅₀ of 4.1 gm./kg.

The skin penetration LD₅₀ is believed to be numerically lower than it should be. The same mortality was encountered in rabbits at 0.63 ml./kg. as at 4 times this level. The range of the LD₅₀ value indicates the lack of precision. By calculation on observed mortality the LD₅₀ is 1.3 (0.32 to 4.9) ml./kg. The LD₅₀ for trimethyl tetrahydrobenzaldehyde is over 10 times this value, namely: 15.8 ml./kg.

Substantially saturated vapor was lethal to rats in 8 hours but not in 4 hours. Known concentrations gave conflicting results probably because of heat degradation during vaporization for the preparation of the vapor-air mixtures. The hazard by inhalation is slight and its warning properties are good.

Tetrahydrobenzaldehyde is only slightly irritating to rabbit skin but it burns rabbit eyes to the same extent as acetone, which is a member of Grade 5.

Sample

An 8-ounce sample labelled 1,3,4,6-tetrahydrobenzaldehyde was received 8-31-53 under identification #245 RD 5. Toxicity studies were requested by Dr. G. W. Nelson.

Single Oral Doses

The LD₅₀ for male albino rats fed a 10% dilution in corn oil is 2.5 (2.2 to 2.7) gm./kg.

Carworth-Wistar, non-fasted rats, 5 to 6 weeks of age and 90-120 grams in weight were dosed at levels differing by a factor of 1.26 in a geometric series. The rats were reared in our own colony and maintained from time of weaning on Rockland ratd diet (complete). Thompson's method of calculating the median-effective dose (LD₅₀) was applied to the 14-day mortality data.