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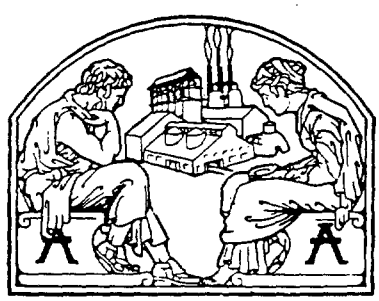

RANGE-FINDING TOXICITY DATA FOR 43 COMPOUNDS

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FOREWORD

Individually, the short-term toxicological research findings presented herein did not merit consideration for publication. Summarized, in tabular fashion, however, such findings have made useful contribution to the toxicological literature.

Sponsors of this research have agreed to collective publication of these findings, and it is hoped that their example will be followed by others in industry. It is becoming increasingly apparent that such data lying dormant in industry's files serves no one.

Undoubtedly, much information which exists will, upon careful study, be found unsuitable for publication for one reason or another (e.g., results on proprietary mixtures of compounds). The Foundation's staff and Chemical-Toxicological Committee are prepared to receive data from individual companies in order to help develop sufficient data for other similar bulletins in this series from time to time.

Steps are also under way to develop better information from human exposure to known concentrations of potentially toxic materials to help validate threshold standards set on data from animal experiments. Much of the human data will be negative and will never become published, but must be maintained in a systematic manner nevertheless.

Extensive cooperation of industry is prerequisite to further progress and is earnestly solicited.

ACKNOWLEDGMENTS

Many persons have contributed through their technical performance to the results obtained. In particular, the authors acknowledge the work of Dr. Marion Westrick and Mr. James McNerney. The Research Laboratory is under the direction of Dr. Paul Gross.

RANGE-FINDING TOXICITY DATA FOR 43 COMPOUNDS*

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Introduction:

Range-finding toxicity tests have been performed by the Research Laboratory of the Industrial Hygiene Foundation for a number of years. A part of these data have now been made available for publication.

Smyth and Carpenter[1] introduced the range-finding test in the industrial laboratory and have presented data on several hundred materials.[2-6] Their description of the role of range-finding tests bears repetition here:

". . . the range-finding test is relied on only to allow predictions of the comparative hazards of handling new chemicals. Acute toxicity studies, no matter how precisely executed, yield no more than an indication of the degree of care necessary to protect workers or lead to an opinion that certain technically feasible applications of a chemical may or may not eventually be proved safe."

This type of toxicity test procedure is utilized to obtain information for precautionary labeling of hazardous household chemicals. Regulations pursuant to the Federal Hazardous Substances Labeling Act delineate toxicity testing procedures which shall be required for chemicals contained in household substances. In order to facilitate such toxicity tests the Committee on Toxicology

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*The toxicity data summarized in the report was obtained in part by the following members of the Foundation: Celanese Corporation, Koppers Company, Inc., and Pittsburgh Plate Glass Company.

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of the National Academy of Sciences-National Research Council has provided a publication titled, "Principles and Procedures for Evaluating the Toxicity of Household Substances."[7]

The purpose of this manuscript is to make available data where none has been previously published, or to allow comparisons where others may have studied the same material.

Methods and Results:

The methods for obtaining the range-finding data of this presentation are generally consistent with the NAS-NRC publication.[7] Variations which may be considered important are indicated by appropriate footnotes. Compounds are listed according to their chemical grouping in Table 1.

Table 1

RANGE-FINDING TOXICITY DATA

Material	Single Oral LD_{50}-Rats (gm/kg)[a]	Single Skin Pen. LD_{50}-Rabbits (gm/kg)[a]	Inhalation by Rats Conc.	Time	Mortality	Irritation to Rabbit Skin (Draize Units)	Irritation to Rabbit Eye (Draize Units) Conj.	Iris	Cornea
Hydrocarbons & Substituted Hydrocarbons:									
1-Chloromethyl-naphthalene	0.89	2.00	0.44mg/l[c] 0.52mg/l[c]	1 hr. 1 hr.	0/5 0/5	—	—	—	—
1, 3, 5-Hexatriene	0.21	6.73	100,000 ppm (approx.)	30 min. 15 min. 5 min.	6/6 6/6 1/6	Negative[b]	Slight[b]	Slight[b]	Negative[b]
Hydroxy Compounds:									
4-Acetylresorcinol (2, 4-Dihydroxy-acetophenone)	2.83	>3.98	—	—	—	0	Severe[b]	Severe[b]	Severe[b] but Reversible
p-t-Amylphenol	1.83	>3.16	—	—	—	Corrosive	Severe[b]	Severe[b]	Severe[b]
6-t-Butyl-3, 4-xylenol	1.03	0.71	—	—	—	Corrosive	24 hr. 17/20 48 hr. 17/20 72 hr. 17/20	5/10 5/10 5/10	40/80 60/80 56/80
6, 6'-Butylidene bis (2, 4-xylenol)	5.50	>3.98	—	—	—	0	24 hr. 4/20 48 hr. .4/20 72 hr. 0/20	0/10 0/10 0/10	.2/80 0/80 0/80
p-t-Butylphenol	5.66	>3.16	—	—	—	Corrosive	Severe[b]	Severe[b]	Severe[b]
dl,-2,3,-Dibromo-1,4-butanediol	2.46	>2.00	—	—	—	0	24 hr. 16/20 48 hr. 10/20 72 hr. 8/20	5/10 5/10 5/10	20/80 19/80 19/80

See end of table for footnotes.

RANGE-FINDING TOXICITY DATA (Continued)

Material	Single Oral LD_{50}- Rats (gm/kg)[a]	Single Skin Pen. LD_{50}- Rabbits (gm/kg)[a]	Inhalation by Rats Conc.	Time	Mortality	Irritation to Rabbit Skin (Draize Units)	Irritation to Rabbit Eye (Draize Units) Conj.	Iris	Cornea
Hydroxy Compounds: (Con't)									
dl, -2, 3-Dichloro-1, 4-butanediol	2.83	>2.00	—	—	—	0.5	24 hr. 16/20 48 hr. 12/20 72 hr. 11/20	5/10 4/10 5/10	20/80 34/80 40/80
Diresorcyl Sulfide	4.29	—	—	—	—	0	Severe[b]	Severe[b]	Severe[b]
2, 4-Di-t-amyl-phenol	0.33	>3.16	—	—	—	Corrosive	Moderate[b]	Moderate[b]	Slight[b]
1, 6-Hexanediol	7.13	>3.98	—	—	—	0	24 hr. 11/20 48 hr. 10/20 72 hr. 9/20	5/10 3/10 3/10	4/80 3/80 3/80
2, 2'-Methylene bis (4, 6-di-t-butyl-3-methylphenol)	>20.00	>3.98	—	—	—	0	24 hr. 2/20 48 hr. 0/20 72 hr. 0/20	0/10 0/10 0/10	0/80 0/80 0/80
2, 2'-Methylene bis (6-t-butyl-3, 4-xylenol)	>20.00	>3.98	—	—	—	0	24 hr. 1/20 48 hr. .4/20 72 hr. 0/20	0/10 0/10 0/10	0/80 0/80 0/80
6-t-Octylamino-methyl-4-benzoyl resorcinol	>5.00	—	—	—	—	—	24 hr. 1/20 48 hr. .6/20 72 hr. 0/20	0/10 0/10 0/10	0/80 0/80 0/80
n-Propanol	5.40	6.73	20,000 ppm 20,000 ppm	1 hr.[f] 1 hr.[f]	0/5 0/5	0	24 hr. 16/20 48 hr. 16/20 72 hr. 15/20	5/10 4/10 4/10	19/80 22/80 27/80
Resorcinol, Flaked Grade	0.98	3.36	—	—	—	4.4	24 hr. 20/20 48 hr. 20/20 72 hr. 20/20	5/10 5/10 5/10	80/80 80/80 80/80
2, 6-Xylenol	0.4	1.00	—	—	—	Corrosive	24 hr. 15/20 48 hr. 14/20 72 hr. 13/20	5/10 5/10 5/10	40/80 40/80 40/80

See end of table for footnotes.

RANGE-FINDING TOXICITY DATA (Continued)

Material	Single Oral LD_{50}-Rats (gm/kg)[a]	Single Skin Pen. LD_{50}-Rabbits (gm/kg)[a]	Inhalation by Rats Conc.	Time	Mortality	Irritation to Rabbit Skin (Draize Units)	Irritation to Rabbit Eye (Draize Units) Conj.	Iris	Cornea
Acids:									
9, 9'-Fluorenedi-propionic Acid	2.14	—	—	—	—	0	Slight[b]	Negative[b]	Negative[b]
Norcamphoric Acid	3.25	>3.98	—	—	—	2.0	24 hr. 13/20 48 hr. 14/20 72 hr. 13/20	5/10 5/10 5/10	40/80 50/80 35/80
Aldehydes:									
Diphenaldehyde (2, 2'-Diformyl-biphenyl)	2.83	—	—	—	—	Moderate[b]	Severe[b]	Severe[b]	Severe[b]
Paraformaldehyde	1.55	—	—	—	—	—	—	—	—
Esters:									
Dibutyl Norcam-phorate	6.30	>15.8	0.025 mg/l[c]	8 hrs.	0/6	0	24 hr. 0/20 48 hr. 0/20 72 hr. 0/20	0/10 0/10 0/10	0/80 0/80 0/80
Dimethyl Norcam-phorate	—	—	—	—	—	0	Severe[b]	Severe[b]	Severe[b]
Ethyl α-(hydroxy-methyl) acrylate	0.62	0.36	150ppm[c] (approx.)	8 hrs.	0/6	Moderate[b]	Severe[b]	Severe[b]	Severe[b]
1% in water	—	—	—	—	—	Negative[b]	Slight[b]	Negative[b]	Negative[b]
Isopropyl Chloroformate	1.07	11.3	—	—	—	Slight[b]	Severe[b]	Severe[b]	Severe[b]
Isopropyl Percarbonate	2.14	—	—	—	—	—	—	—	—
45% in 1:1 Benzene-Cyclohexane	6.5	4.0 ml/kg	—	—	—	Corrosive[b]	Severe[b]	Severe[b]	Severe[b]

See end of table for footnotes

RANGE-FINDING TOXICITY DATA (Continued)

Material	Single Oral LD_{50}-Rats (gm/kg)[a]	Single Skin Pen. LD_{50}-Rabbits (gm/kg)[a]	Inhalation by Rats Conc.	Time	Mortality	Irritation to Rabbit Skin (Draize Units)	Irritation to Rabbit Eye (Draize Units) Conj.	Iris	Cornea
Esters: (Con't)									
Propylene Glycol Monoacrylate	0.59	—	—	—	—	—	—	—	—
Tri-β-Chloro-ethylphosphate	1.23	—	—	—	—	—	—	—	—
Ethers:									
2, 3, 5, 6-Tetrachlor-onitroanisole	0.26	3.36	111 mg/m^3[e]	7 hrs.	0/5	—	—	—	—
Trimethylolpro-pane Diallyl Ether	6.50	>15.8	—	—	—	—	—	—	—
Trimethylolpro-pane Monoallyl Ether	4.93	>15.8	—	—	—	—	—	—	—
Amines & Nitrogen Compounds:									
9, 9'-Fluorenedi-propionitrile	2.18	—	—	—	—	0	Negative[b]	Negative[b]	Negative[b]
9, 9'-Fluorene-dipropylamine	0.62	—	—	—	—	Corrosive	Severe[b]	Severe[b]	Severe[b]
10% in water	—	—	—	—	—	—	Severe[b]	Severe[b]	Severe[b]
1% in water	—	—	—	—	—	—	Severe[b]	Severe[b]	Severe[b]
Indene Tripropyl-amine	0.54	0.50	—	—	—	Corrosive	24 hr. 20/20 48 hr. 20/20 72 hr. 20/20	5/10 5/10 5/10	74/80 80/80 80/80
Isopropyl N-(3-Chlorophenyl) Car-bamate	5.0-7.5[d]	—	—	—	—	—	—	—	—

See end of table for footnotes.

RANGE-FINDING TOXICITY DATA (Continued)

Material	Single Oral LD50-Rats (gm/kg)[a]	Single Skin Pen. LD50-Rabbits (gm/kg)[a]	Inhalation by Rats Conc.	Time	Mortality	Irritation to Rabbit Skin (Draize Units)	Irritation to Rabbit Eye (Draize Units) Conj.	Iris	Cornea
Amines & Nitrogen Compounds: (Con't)									
N, N, N', N'-Tetrakis (2-dihydroxyboroxy-propyl) ethylene-diamine	4.93	>3.98	—	—	—	0	24 hr. 1/20 48 hr. 0/20 72 hr. 0/20	0/10 0/10 0/10	0/80 0/80 0/80
Miscellaneous:									
1, 2-Bis (3, 7-dimethyl-5-n-butoxy-1-aza-5-bora-4, 6-dioxocyclooctyl-1) ethane	5.66	>3.98	—	—	—	5.0	24 hr. 9/20 48 hr. 8/20 72 hr. 5/20	2/10 2/10 2/10	20/80 20/80 20/80
dl-Butadiene Dioxid	0.21	0.80	56 ppm	4 hrs.	LC_{50}	—	—	—	—
Diketene	0.54	6.73	200 ppm 20,000 ppm	1 hr. 1 hr.	0/10 10/10	4.9	24 hr. 20/20 48 hr. 20/20 72 hr. 20/20	5/10 5/10 5/10	70/80 70/80 60/80
2-Hydroxymethyl-2'-carboxybiphenyl	6.50	—	—	—	—	0	Moderate[b]	?[b]	Slight[b]
Phthalazone	0.37	>3.98	—	—	—	0	Slight[b]	Negative[b]	Negative[b]
Trioxane	8.19	>3.98	—	—	—	0	24 hr. 9/20 48 hr. 6/20 72 hr. 4/20	2/10 1/10 0/10	6/80 2/80 2/80

a - Values indicated by > represent the largest dose administered, and there was no mortality at this level.
b - No Draize Scores obtained. Designations of grade based on description of effect rather than quantitative comparisons. In the case of eye tests, 0.5 ml of material was administered rather than 0.1 ml as in present Draize method.
c - Saturated Vapor
d - No constant ratio between dosage levels.
e - Material mixed with Kaolin (73 mg/m³) to produce a dust cloud. Total concentration of TCNA-Kaolin - 184 mg/m³.
f - Static Exposure

Discussion:

The toxic doses and irritation scores given in Table 1 for various materials represent quantitative results on animals from specified test procedures. To the person familiar with the procedures, the doses and scores have approximate meanings in terms of hazard to man. However, in the interest of providing guidelines to persons unfamiliar with extrapolation of animal data, it was felt worthwhile to make some interpretive comments.

With respect to toxicity, from swallowing, skin penetration and inhalation, Hodge and Sterner[8] have suggested the use of toxicity classes with a commonly used designation for certain dose ranges and have indicated a probable lethal oral dose for man on the basis of animal data. If data on humans indicate a variance, either positively or negatively, such data will, of course, take precedence. The Hodge and Sterner tabulation of toxicity classes is given in Table 2.

The Federal Hazardous Substances Labeling Act makes use of a slightly different grouping of toxic doses. It designates as "highly toxic" those substances wherein, for half or more than half of a statistically significant group of animals, the lethal oral dose to rats is 50 mg/kg or less, the lethal dermal penetration in rabbits is 200 mg/kg or less, and the lethal concentration to rats exposed for one hour is 200 ppm or less by volume of gas or vapor or 2 mg/l or less of mist or dust. Further, it designates as "toxic" those substances with lethal doses greater than those of the "highly toxic" category but less than 5 gm/kg for oral doses to rats, less than 2 gm/kg for dermal penetration on rabbits, and less than 20,000 ppm by gas or vapor or less than 200 mg/l of mist or dust for rats exposed for one hour.

Table 2

COMBINED TABULATION OF TOXICITY CLASSES*[8]

Various Routes of Administration				
Commonly Used Term	LD_{50} Single Oral** Dose Rats	Inhalation 4 hr Vapor Exposure Mortality 2/6-4/6 Rats	LD_{50} Skin Rabbits	Probable Lethal Dose for Man
Extremely toxic	1 mg or less per kg	10 ppm	5 mg or less per kg	A taste, 1 grain
Highly toxic	1-50 mg	10-100	5-43 mg	1 tsp. 4 cc
Moderately toxic	50-500 mg	100-1000	44-340 mg	1 ounce 30 gm
Slightly toxic	0.5-5 g	1000-10,000	.35-2.81 g/kg	1 pint 250 gm
Practically non-toxic	5-15 g	10,000-100,000	2.82-22.59 g/kg	1 quart
Relatively harmless	15 g and more	100,000	22.6 or more g/kg	> 1 quart

* Hodge, H.C. and Sterner, J. H. American Industrial Hygiene Association Quarterly, 10:4, 93, Dec. 1943.

** Standards for intravenous LD_{50} for rats and rabbits may be obtained approximately by dividing the oral toxicity standards for rats by 10.

With respect to interpretation of dermal irritation scores, materials tested by the prescribed techniques of the FHSLA and yielding Draize scores of 5.0 or greater are designated "primary irritants" and must bear appropriate labeling if they are considered "household chemicals." The practice of labeling industrial chemicals follows the same criterion in general. Draize scores of less than 5.0 merely show the relative irritation potential. While not standardized, some toxicologists have utilized an arbitrary procedure wherein a score of less than 0.5 is insignificant, 0.5-2.0 represents mild irritation, 2.0-5.0 represents moderate irritation, and greater than 5.0 represents severe irritation.

A corrosive substance is one that causes visible destruction or irreversible alterations in the tissue at the site of contact. A substance would be considered corrosive either by human experience that tissue destruction occurs or, if when tested on rabbits by the Draize technique discussed above, the animal skin is destroyed or irreversibly changed in 24 hours or less.

The scoring of eye irritation tests is rather complicated and a complete explanation here might be more confusing than helpful. Perhaps it will be sufficient to suggest that any effect on cornea or lens represents an undesirable condition and average scores of 10/20 or greater for the conjunctivae represent fairly intense irritation. One must not, however, overlook the importance of progression of scores with time. While one material may produce an effect which is rapidly reversible with the eye regaining normal or near normal appearance within 48 to 72 hours, another material may not recover but may become worse with time.

All of the above points, oral toxicity, dermal toxicity, inhalation toxicity, dermal irritation and eye irritation, need to be considered in the assessment of potential hazard from a chemical and the need for caution and/or protective equipment during handling. The likelihood of contact and possible damage must be postulated in terms of the use (amounts and frequency) and toxic or irritant potential of the substance. Each manufacturer and user of hazardous substances must analyze his own process and draw his own conclusions (possibly with the help of qualified industrial hygiene personnel).

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