DEPOSITION EXHIBIT 22 KELLY

Tabulation of Toxicity Classes

A Report Prepared by
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from Notes Taken at the Toxicological Round-Table

THE discussions of the Toxicological Round-Table during the past three years have been based on the recognized need for a healthy degree of standardization in toxicological terminology and in methods of testing. There have been several aspects of the development of this idea. One of these concerns the classification of degrees of toxicity; the current report summarizes our thinking and points out some of the needed further developments. We have taken it upon ourselves to prepare this summary for a group which included the following: H. F. SMYTH, C. P. CARPENTER, D. D. IRISH, V. K. ROWE, W. B. DEICHMANN, J. H. DRAIZE, W. F. VON OETTINGEN, C. I. BLISS, O. M. GRUHZIT, H. BRIEGER, E. A. MAYNARD, E. M. ADAMS, R. A. KEHOE, F. F. HEYROTH, L. T. FAIRHALL, L. C. MILLER, H. E. STOKINGER, A. J. LEHMAN, F. R. HOLDEN, and others.

At the A.I.H.A. meeting in April, 1947, in Buffalo, a series of terms was proposed to describe the toxicity of industrially-important chemicals. These terms were to be given a special technical significance so that —among industrial toxicologists—dosage and descriptive terms would be codified. Six ranges of toxicity beginning with the most toxic compounds might be described as follows: (1) extremely toxic, (2) highly toxic, (3) moderately toxic, (4) slightly toxic, (5) practically non-toxic, and (6) relatively harmless. To give these categories a significant reference, the probable lethal dose for man in common units of measurement are given in the accompanying table.

It is obvious that if a drop or a grain of any substance is capable of causing death, it is 'extremely toxic.' The next common unit of measurement is a teaspoonful. A substance which in this small dosage would cause death would certainly be 'highly toxic.' If an ounce were required, it seems reasonable to describe such a material as 'moderately toxic,' whereas a lethal dose of a pint might be described as 'slightly toxic' and a quart as 'practically non-toxic.' There are relatively few materials in which a lethal dose is greater than a quart and it seems that such material could properly be designated as 'relatively harmless.' In other words, the descriptive terms logically and easily fit the amounts commonly dealt with as units of measurement. What we propose is that for various routes of administration, for example, orally, intraperitoneally, by lung, or by skin, and for specifically stated species, these common terms be defined *by industrial toxicologists* as referring specifically to doses effective within the defined ranges.

The industrial toxicologist has at least two problems in describing the poisonous character of chemicals handled in his plant. In the first place he must describe the toxic properties in some simple way that is understandable to other toxicologists. Since this tabulation of toxicity classes was first made a little over a year ago, it has been applied to results of toxicity testing and has been found to fill, at least for us, a long-felt need for a simple, understandable expression of the degree of toxicity. It not only has helped as a descriptive language but, in comparing the results of toxicity tests on a sizable list of compounds, these categories have materially assisted in organizing and presenting the data.

The second problem which the industrial toxicologist continuously faces is his responsibility to the plant operators and management in the translation of toxicity data into terms of 'hazard.' This translation must be in terms that will immediately and clearly describe the precautions to be used in handling the material. One very active laboratory has used the device of naming toxic substances in each hazard category so that when a new substance is investigated, it is only necessary to relate it to the few well-known materials, the handling properties of which are well-established. Since only rarely would such 'common denominator' or 'reference' compounds have

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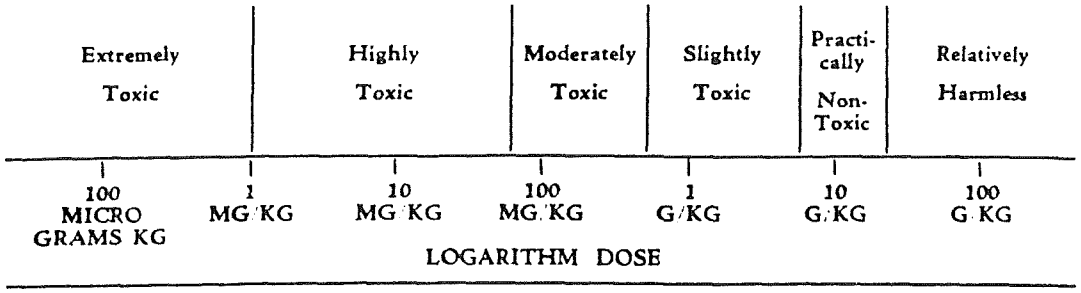
GRAPH OF TOXICITY CLASSES



sufficient familiarity from industry to industry, we would suggest that the typical substances—if selected to represent handling properties—should be so simple and so widely available that each laboratory and plant could recognize the special properties of these substances without extensive investigation. *For the purpose of this discussion, we wish to disregard the categories of 'hazard' and to restrict attention solely to those of 'toxicity.'*

The selection of the exact numerical dosage in mg/kg which defines the ranges corresponding to the terms are arbitrarily chosen. There probably would be as many ranges as people who would select them. In the accompanying figure, the ranges are plotted graphically on a logarithmic scale and it can readily be seen that the various categories, while differing somewhat, are surprisingly comparable in length. This reasonably regular division of the logarithmic range coupled with the fact that the probable lethal dose for man, progressing from a drop or grain to more than a quart, is the approximate mid point of each division, would seem to us a practical division of the toxicity scale. See text table.

At the A.I.H.A. meeting in Boston in April, 1948, the tabulation was discussed briefly and the need for a compilation of information already available in the literature was clearly indicated. During the past year, DR. ROBIN RANKOW has been collecting specific data in a literature survey; the accompanying tables have been prepared by him. These are offered, not as ideal examples, but as the best at hand. They are offered in the hope that these tabulations will provide the opportunity for better type substances to be suggested.

TEXT TABLE

Toxicity Rating	Category	Single Oral Dose	Probable Lethal Dose for Man
1	Extremely toxic	1 mg or less/kg	A taste 1 grain
2	Highly toxic	1—50 mg	1 tsp. 4 cc
3	Moderately toxic	50—500 mg	1 oz. 30 g
4	Slightly toxic	0.5—5 g	1 pint 250 g
5	Practically non-toxic	5—15 g	1 quart
6	Relatively harmless	15 g and more	> 1 quart

The table on oral administration gives the LD_{50} doses for rats in g/kg. Sodium fluoroacetate was the best example of an extremely toxic substance. In fact, very few substances were found of which less than a mg/kg was rapidly fatal. The highly toxic substances, sodium fluoride and ethylene imine, are believed to be widely known as are most of the examples given in the other categories. Comparative data from a few other species are included.

The same terms have been applied to the description of intraperitoneal administration, with, however, a shift of dosage toward smaller values by a factor of 2 to 10 (or approximately one class unit). This relationship was chosen arbitrarily on the basis of limited data and may well need revision when more evidence is accumulated.

The compounds listed in the table covering lethal effects after intraperitoneal administration are duplicates, in some cases, of those in the oral toxicity table. This was felt to be a desirable feature. The exact toxicity of aminopterin in rats is a needed figure. The highly toxic nitrogen mustards were selected as the type substances for this category and it is interesting to note that mustard gas and di-isopropyl fluorophosphate, two of the moderately toxic substances, are also chemical warfare agents. The other compounds listed are, in

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ORAL ADMINISTRATION (GM/KG)

Category	Rats	Other Species
Extremely toxic	Sodium fluoroacetate (0.0001)[1]	Sodium fluoroacetate (50 μg); dogs[1]
Highly toxic	NaF (0.047)[2] Ethylene imine (0.015)[3]	NaF (0.023—0.90); rabbits[12] NaF (0.05—0.1); dogs[12]
Moderately toxic	DDT (10% in oil—0.3)[4] 4, 6 dinitro-o-cresol (0.05)[5]	Acetanilid (0.25); cats[6] DDT (5% in oil—0.3); cats, rabbits[12]
Slightly toxic	Acetanilid (0.8)[6]	Acetanilid (1.5); rabbits[6] Acetanilid (1.4—1.5); guinea pigs[6] Acetanilid (0.75—1.0); dogs[6]
Practically non-toxic	PABA (Para aminobenzoic acid) (>6)[1] Diethylene glycol monoethyl ether (30.6)[7]	PABA (1—3); dogs[1] PABA (2.85); mice[1]
Relatively harmless	Di (2-ethyl hexyl) phthalate (30.6)[9]	Di-2 ethyl hexyl phthalate (33.9); rabbits[9]

1. CHENOWETH and ST. JOHN: *J. Pharm. Exp. Therap.*, 89:76, 1947. 2. ROHOLM, K.: "Fluorine Intoxication." Lewis & Co., Ltd., London, 1937. 3. SMYTH et al: *J. Ind. Hyg. & Tox.*, 23:259, 1941. 4. PHILIPS and GILMAN: *J. Pharm. Exp. Therap.*, 86:87, March, 1946. 5. SPENCER et al: *J. Ind. Hyg. & Tox.*, 30:10 1948. 6. MUNCH, PRATT and PHILLIPS: *J. Am. Pharm. Assn.*, 30:91, 1941. 7. HANZLIK, P. J., et al: *J. Ind. Hyg. & Tox.*, 29:190, 1947. 8. SCOTT et al: *Proc. Soc. Exp. Biol. & Med.*, 49:184, 1942. 9. SHAFFER et al: *J. Ind. Hyg. & Tox.*, 27:130, 1945. 10. CHENOWETH and ST. JOHN: op. cit. 11. LEAKE, C. D.: *J. Pharm.*, 33:279, 1928.

INTRAPERITONEAL ADMINISTRATION (GM/KG)

Category	Rats	Other Species
Extremely toxic	Aminopterin	
Highly toxic	Nitrogen mustards (0.0005—0.001)[15]	Nitrogen mustards (0.001—0.002); mice, rabbits[15]
Moderately toxic	NaF (0.013—0.016)[1] Mustard gas (0.003)[17] Di-isopropyl fluorophosphate (0.0002)[16]	NaF (0.23—0.045); dogs, rabbits[1] Mustard gas (0.006—0.008); mice, rabbits[17] Di-isopropyl fluorophosphate (0.0004—0.003): monkeys, mice, rabbits, cats, dogs[16]
Slightly toxic	Ethylene chlorohydrin (0.05—0.06)[3] Methyl bromide (0.12—0.28)[6] BAL (0.105)[12]	Diethyl phthalate (I.V., 0.1); rabbits[9] Phthalic acid (0.55); mice[10] BAL (0.1); mice[14]
Practically non-toxic	Acetaldehyde (0.5)[2] Choline (0.29—0.34)[3] PABA (P-aminobenzoic acid) (4.0)[11]	Choline (0.32); mice[4] PABA (I.V., 2.0); rabbits[12]
Relatively harmless	Diethyl phthalate (30.7)[7]	Diethyl hexyl phthalate (128); mice[8]

1. ROHOLM: "Fluorine Intoxication." Lewis & Co., Ltd., London, 1937, p. 16. 2. STOTZ, WESTERFELD, and BERG: *J. Biol. Chem.*, 152:41, 1944. 3. HODGE: *Proc. Soc. Exp. Biol. & Med.*, 57:26, 1944. 4. HODGE and GOLDSTEIN: *Proc. Soc. Exp. Biol. & Med.*, 51:281, 1942. 5. GOLDBLATT: *Brit. J. Ind. Med.*, 1:213, 1944. 6. MILLAR and HAGGARD: *J. Ind. Hyg. & Tox.*, 25:423, 1943. 7. SHAFFER, CARPENTER, and SMYTH: *J. Ind. Hyg. & Tox.*, 27:130, 1945. 8. FLURY and WIRTH: *Arch. Gewerbepath.*, 5:1, 1933. 9. HODGE, H. C.: *Proc. Soc. Exp. Biol. & Med.*, 53:20, 1943. 10. HODGE et al: *Proc. Soc. Exp. Biol. & Med.*, 49:471, 1942. 11. RICHARDS: *Fed. Proc.*, 2:71, 1942. 12. ANIGSTEIN and BADER: *Science*, 101:591, 1942. 13. WATERS and STOCK: *Science*, 102:601, 1945. 14. GRAHAM and HOOP: *Brit. J. Pharm. & Chemother.*, 3:84, 1948. 15. ANSLOW et al: *J. Pharm. & Exp. Therap.*, 91:224, 1947. 16. HORTON et al: *J. Pharm. & Exp. Therap.*, 87:414, 1947. 17. KARNOVSKY et al: *J. Pharm. & Exp. Therap.*, 93:1, 1948.

INHALATION — 4-HOUR VAPOR EXPOSURE
(Original Classes by H. F. Smyth & colleagues)

Category	Rats	Other Species
Extremely toxic	Ethylene imine (25—100 p.p.m.)[9]	Ethylene imine (10+ p.p.m.); guinea pigs[9]
Highly toxic	Phosgene (50—500 p.p.m.)[6] Nitrogen oxides (30—1000 p.p.m.)[2]	Nitrogen oxides (30—1000 p.p.m.); mice, guinea pigs, rabbits, cats[2]
Moderately toxic	Vinyl cyanide (153 p.p.m.)[3] HCN (200—480 p.p.m.)[7] SO_2 (400—3000 p.p.m.)[7] Methyl bromide (about 500 p.p.m.)	Vinyl cyanide (153 p.p.m.); guinea pigs, rats, monkeys, dogs[3]
Slightly toxic	Ethylene dichloride (1, 2 dichloroethane) (3000 p.p.m.)[1]	Ethylene dichloride (3000 p.p.m.); rabbits, guinea pigs, mice[1]
Practically non-toxic	Acetone (40,000 p.p.m.)[10]	Isopropyl benzene (2000 p.p.m.); mice[4]
Relatively harmless	Freon	Acetone (20,600 p.p.m.); mice[5]

1. HEPPEL et al: *J. Pharm. Exp. Therap.*, 84:53, 1945. 2. LA TOWSKY, MACQUIDDY, and TULLMAN: *J. Ind. Hyg. & Tox.*, 23:129, 1941. 3. DUDLEY, SWEENEY and MILLER: *J. Ind. Hyg. & Tox.*, 24:255, 1942. 4. WERNER, DUNN, and VON OETTINGEN: *J. Ind. Hyg. & Tox.*, 26:264, 1944. 5. SAYERS et al: U.S.P.H.S. Bull. No. 185, 1929. 6. U. S. War Department, Medical Dept., U.S.A. (Vol. XIV), "Medical Aspects of Gas Warfare," 1926. 7. SAYERS, DALLA VALLE, and YANT: *Ind. Eng. Chem.*, 26:1251, 1934. 8. FIELDNER, KATZ, and KINNEY: U. S. Bur. Mines, Techn. Papers, 272, 1921. 9. CARPENTER, SMYTH, and SHAFFER: *J. Ind. Hyg. & Tox.*, 30:2, 1948. 10. HAGGARD, GREENBERG, and TURNER: *J. Ind. Hyg. & Tox.*, 26:133, 1944.

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TABULATION OF TOXICITY CLASSES
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LAWYER'S NOTES

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