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CONCENTRATION—TIME MORTALITY RESPONSE RELATIONSHIP OF IRRITANT AND SYSTEMICALLY ACTING VAPOURS AND GASES

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Summary

This report presents the re-evaluation of the raw data of previously published acute inhalation toxicity studies of some volatile industrial chemicals. In these studies both concentration and exposure time were varied. The raw data were obtained from an extensive literature search and were subjected to probit analysis. The results show that the product of concentration and exposure time (ct) is not always a good parameter for predicting the mortality response (Haber's rule). On the contrary, the term $c^n t$, in which the exponent n is different from 1, often predicts the response very well.

Introduction

Knowledge of the acute inhalation toxicity of volatile chemical products is desirable for purposes of risk analysis. In this study the scientific literature on acute inhalation toxicity of volatile chemicals was examined. Only those studies in which the raw data were presented and in which both concentration and exposure time were varied are included here. About 20 studies were selected, on a comparable number of locally and systemically acting agents. Thus a comparison of mortality response relationships between compounds with either local or systemic action was possible.

The raw data were re-evaluated by the method of probit analysis as described by Finney [1]. The method of probit analysis was first introduced between 1940 and 1950, but never became popular among toxicologists. The mathematical operations were complicated and time consuming if performed by hand. However, simple home computers can now be programmed to perform probit analysis. In addition, if more than one independent variable is studied in relation to the mortality response, probit analysis is the only way to optimize interpretation of the raw data.

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The method of probit analysis

The basis of this method is the assumption that the mortality response, plotted against the logarithm of the concentration or against the logarithm of the exposure time, has the shape of a cumulative normal distribution. This is expressed in the following equations:

$$Y = b_0 + b_1 \ln c + b_2 \ln t \tag{1}$$

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{y-5} \exp\left(-\frac{1}{2}u^2\right) du \tag{2}$$

where, Y = probit (= standard normal deviate + 5), P = mortality response, c = exposure concentration, t = exposure duration, b_0 = regression coefficient, b_1 = regression coefficient, and b_2 = regression coefficient.

The regression coefficients in eqn. (1) are derived from the raw data using the method of Maximum Likelihood [1]. This method yields the best estimate and in addition the variances and covariances of the regression coefficients. There is a large degree of mutual correlation between the regression coefficients. Therefore in calculating confidence limits of a LC_{50}, not only variances, but also covariances have to be taken into account [1]. The raw data and mathematical details of the probit analysis are available to interested readers on request.

Results

Probit analysis of the raw data produced the Maximum Likelihood estimates of regression coefficients, variances and covariances. In addition, the chi-square was determined, a measure of the goodness of fit. Generally, the derived probit equations met the requirements of a good fit. In order to avoid the presentation of an enormous amount of data only the Maximum Likeli-

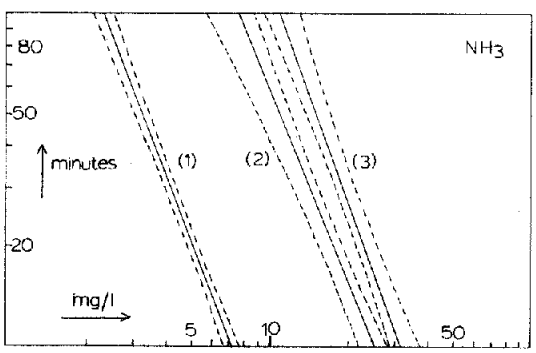

Fig. 1. Exposure of mice (1), male (2) and female rats (3) to ammonia [2–4]; ——: LC_{50}; — — — —: 95% confidence limits.

TABLE 1

Regression coefficients of the concentration—time mortality response relationships of several irritant chemicals for different species according to eqn. (1)

Chemical	Species, sex	Regression coefficients		
		b_0	b_1	b_2
Ammonia [2]	male + female rats	−47.9	4.65	2.30
Ammonia [2]	male rats	−76.2	7.17	3.71
Ammonia [2]	female rats	−62.6	5.91	2.76
Ammonia [3, 4]	mouse	−54.5	5.95	2.89
HCl gas [5]	rat	−47.7	4.06	4.90
HCl aerosol [5]	rat	−29.1	2.77	2.68
HCl gas [5]	mouse	−10.5	1.40	1.16
HCl aerosol [5]	mouse	−22.8	2.51	2.21
Chlorine pentafluoride [6]	rat	−29.3	3.92	2.10
Chlorine pentafluoride [6]	mouse	−15.5	2.42	1.57
Chlorine pentafluoride [6]	dog	−20.8	2.79	1.95
Chlorine pentafluoride [6]	monkey	−17.6	2.87	0.696
Nitrogen dioxide [7]	rat	−15.2	3.09	0.885
Nitrogen dioxide [7]	guinea pig	−10.5	2.63	0.537
Nitrogen dioxide [7]	rabbit	−5.43	1.52	0.352
Nitrogen dioxide [7]	dog	−38.7	6.48	1.97
Nitrogen dioxide [7]	mouse	−35.6	6.43	1.76
Chlorine [8]	mouse	−23.2	3.82	1.10
Perfluoroisobutylene [9]	rat	−14.9	2.87	2.36
Crotonaldehyde [10]	rat	−15.6	2.00	1.72
Hydrogen fluoride [11]	rabbits + guinea pigs	−7.35	1.38	0.71
Ethylene imine [12]	rat	−3.85	0.959	0.714
Ethylene imine [12]	guinea pig	−19.5	2.25	2.58
Bromine [8]	mouse	−24.7	3.13	1.44
Dibutylhexamethylenediamine [13]	rat	−11.7	1.33	1.29

hood estimates of the regression coefficients (b_0, b_1, b_2 of eqn. 1) are presented for each volatile chemical and for each species (see Tables 1 and 2).

In Table 3 some LC_{50} values for exposure durations of 30 min for a limited number of compounds were presented in order to show the difference between mice and other species. Table 4 presents the quotient of b_1 and b_2 (= exponent n, see eqns. (1) and (3) and the Discussion). The b_1 and b_2

TABLE 2

Regression coefficients of the concentration—time mortality response relationship of several systemically acting chemicals for different species according to eqn. (1)

Chemical	Species, sex	Regression coefficients		
		b_0	b_1	b_2
Hydrogen cyanide [14]	goat	−27.3	4.50	2.02
Hydrogen cyanide [14]	monkey	−6.87	1.57	0.835
Hydrogen cyanide [14]	rabbit	−15.6	3.22	0.744
Hydrogen cyanide [14]	rat	−3.27	1.15	0.701
Hydrogen cyanide [14]	cat	−8.26	2.09	0.741
Hydrogen cyanide [14]	dog	−1.30	1.02	0.327
Hydrogen sulphide [15]	cat + rabbit	−42.6	5.13	2.36
Methyl t-butyl ether [16]	mouse	−25.1	3.98	2.02
Methylenechlorobromide [17]	male rats	−45.0	3.56	2.26
Methylenechlorobromide [17]	female rats	−49.1	3.86	2.34
Ethylenedibromide [18]	rat	−32.5	3.12	2.69
Tetrachloroethylene [19]	rat	−39.1	3.34	1.65
Trichloroethylene [20]	rat	−8.36	0.768	0.909
Carbon tetrachloride [21]	rat	−39.4	3.46	1.22
Acrylonitrile [22]	rat	−42.1	3.83	3.74
Acrylonitrile [23]	rat	−165	15.2	11.4

TABLE 3

LC_{50} (30 min) values of a number of volatile chemicals

Species	LC_{50} (30 min) (mg/m^3)				
	NH_3	NO_2	ClF_5	HCl (gas)	HCl (aerosol)
Monkey			1154		
Dog		300	955		
Rabbit		435			
Rat	16300	258	1016	7050	8100
Guinea pig		179			
Mouse	4200	215	528	3830	3273

TABLE 4

Value of the exponent n for several gases and vapours, of which the probit Y of the mortality response in relation to exposure concentration c and exposure period t can be predicted by eqn. (3).

Gas or vapour	Exponent n	95% confidence limits
Local irritants		
NH_3	2.0	(1.6, 2.4)
HCl	1.0	(0.7, 1.3)
ClF_5	2.0	(1.4, 2.6)
NO_2	3.5	(2.7, 4.3)
Cl_2	3.5	(2.5, 4.4)
Perfluoroisobutylene	1.2	(1.1, 1.4)
Crotonaldehyde	1.2	(1.1, 1.3)
HF	2.0	(1.2, 2.8)
Ethylene imine	1.1	(0.8, 1.3)
Br_2	2.2	(2.0, 2.4)
Dibutylhexamethylenediamine	1.0	(0.6, 1.4)
Systemic action		
HCN	2.7	(1.8, 3.7)
H_2S	2.2	(1.6, 2.7)
Methyl t-butyl ether	2.0	(1.0, 2.9)
CH_2ClBr	1.6	(1.4, 1.8)
$C_2H_4Br_2$	1.2	(1.1, 1.2)
C_2Cl_4	2.0	(1.4, 2.6)
C_2HCl_3	0.8	(0.3, 1.4)
CCl_4	2.8	(1.9, 3.7)
Acrylonitrile	1.1	(1.0, 1.2)

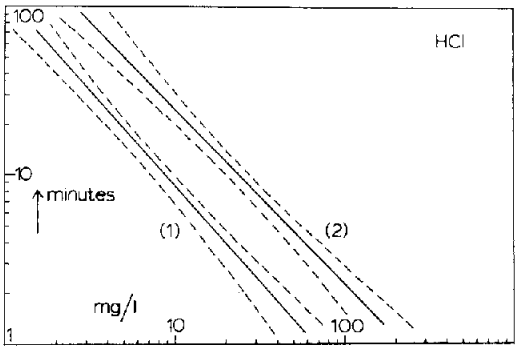

Fig. 2. Exposure of mice (1) and rats (2) to hydrochloric acid aerosol [5]; ——: LC_{50}; — — — —: 95% confidence limits.

values, from which the quotient was derived, were obtained by probit analysis of the data (concentration, exposure time, mortality) of all species together, regardless of sex, for the compound studied. Further, for a limited number of exposures the logarithm of the LC_{50} was plotted against the logarithm of the exposure time with the appropriate confidence limits in Figs. 1 to 7.

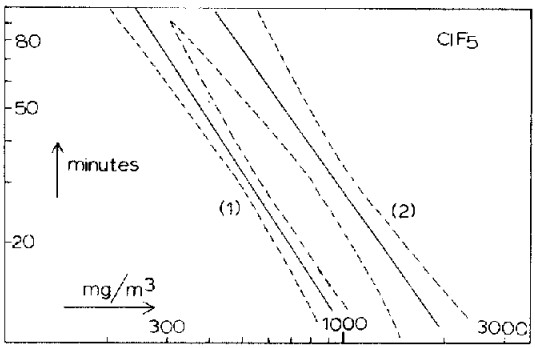

Fig. 3. Exposure of mice (1) and dogs (2) to chlorine pentafluoride [6]; ——: LC_{50}; — — — —: 95% confidence limits.

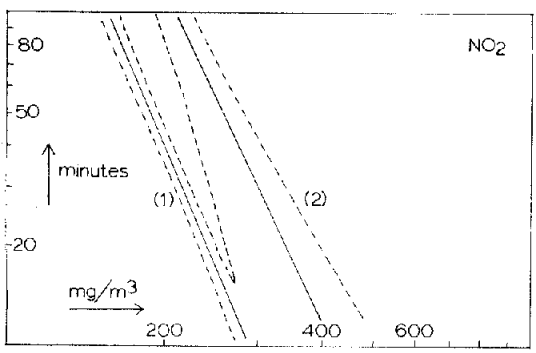

Fig. 4. Exposure of mice (1) and dogs (2) to nitrogen dioxide [7]; ——: LC_{50}; — — — —: 95% confidence limits.

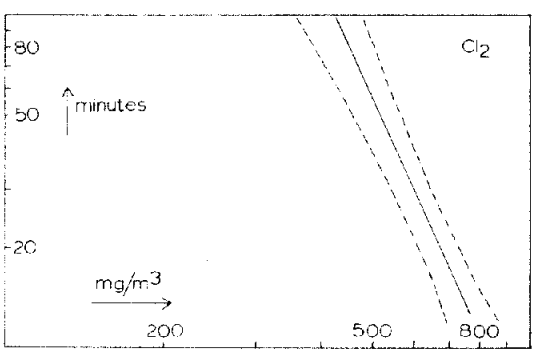

Fig. 5. Exposure of mice to chlorine [8]; ——: LC_{50}; — — — —: 95% confidence limits.

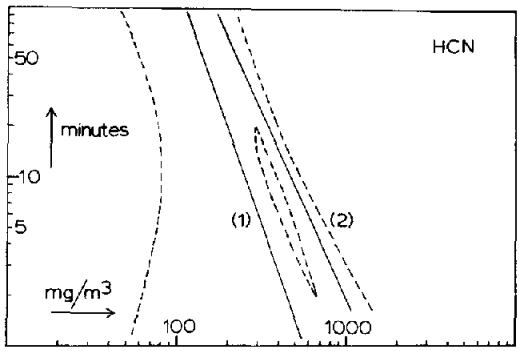

Fig. 6. Exposure of cats (1) and goats (2) to hydrogen cyanide [14]; ——: LC_{50}; — — — —: 95% confidence limits.

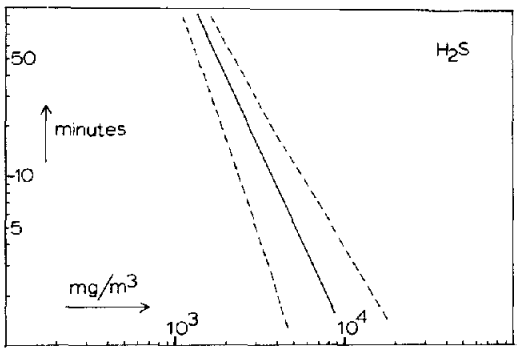

Fig. 7. Exposure of cats and rabbits to hydrogen sulphide [15]; ——: LC_{50}; — — — —: 95% confidence limits.

Discussion

This paper has presented a re-evaluation of previously published data of inhalation toxicity experiments. The method followed is that of probit analysis, which enables a range of concentrations and exposure periods to be associated with any given mortality response. The advantage of this method is that the whole range of parameters concerning acute inhalation toxicity is described by one equation.

Over the range of experiments examined, Haber's rule seems not generally to be obeyed. Haber's rule states that the product of exposure concentration and exposure time controls the mortality response. Regarding eqn. (1) Haber's rule means that regression coefficients b_1 and b_2 should be about equal. It is obvious from the presented regression coefficients b_1 and b_2 in Tables 1 and 2 that they are often not equal. Therefore, Haber's rule does not apply to quite a number of the inhalation toxicity experiments evaluated. The ratio between the regression coefficient of the concentration (b_1) and that of the exposure period (b_2) is of great importance in estimat-

ing the mortality response for exposures in which the concentration varies during the exposure. Therefore eqn. (1) should be rearranged into eqn. (3)

$$Y = b_0 + b_2 \ln [c^n t] \quad (3)$$

$$n = b_1 / b_2$$

The term $c^n t$ may be considered as a dose factor [2, 24—26]. If the concentration varies during the exposure period, this dose factor may be expressed in the form:

$$\int [c(t)]^n \mathrm{d}t$$

where $c(t)$ is the concentration as function of time during exposure.

Table 4 presents the values of the exponent n with the appropriate 95% confidence limit for the compounds of Tables 1 and 2. Both in the case of locally irritant gases and for systemically acting vapours, the exponent n varies greatly and may be considerably greater than one. There appeared to be no obvious difference between systemically and locally acting compounds. This means that a general rule concerning the value of the exponent n does not exist. The exponent should always be derived empirically from acute inhalation toxicity experiments, in which both the concentration and exposure period are variables.

The plots of concentration against exposure period (Figs. 1, 2, 3 and 5) reveal that mice are often more sensitive than other mammals. This is also obvious from the LC_{50} values for an exposure period of 30 min for different species. These were derived from the probit equations and are summarized in Table 3. These findings suggest that experiments using mice do not provide an appropriate basis for predicting quantitatively the mortality response in humans.

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