Environmental Health Perspectives
Vol. 30, pp. 19–21, 1979

Predicting Toxicometric Parameters on the Basis of Studying the Concentration–Time Dependence

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A short-time exposure on the concentration–time relationship base, a classification of substances according to the degree of hazard and the program for assessing safety coefficients have been suggested in order to predict the basic toxicometric parameters (chronic exposure thresholds, maximum allowable concentrations, safety coefficients, and others).

Development of methods for accelerated hygienic-toxicological evaluation of harmful substances, especially of their basic toxicometric parameters, has acquired great importance for preventing chemical pollution of the environment. It has been demonstrated by previous investigations carried out within the framework of cooperation by Soviet and American scientists, that with continuous inhalation of chemical compounds the concentration–time dependence for the appearance of acute effects and physiological and biochemical shifts can be represented by a straight line on a logarithmic scale grid (*1*).

The expression of the "concentration–time" dependence, $\log T = \log T_0 - \tan \alpha \cdot \log C$, indicates that the position of the straight-line curve determines the T_0 parameter (time of occurrence of the effect from exposure to a certain concentration), while the tangent of the angle of incidence ($\tan \alpha$) determines its course on the logarithmic grid. Thus, the curve of the time of occurrence of a certain effect dependent on concentration can be regarded as a regression line of the effect of time on concentration. Moreover, the tangent of the angle of incidence of the curve is the coefficient of regression and indicates the number of times by which the logarithm of the time of occurrence of the effect is increased upon reducing the logarithm of concentration to one.

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In connection with these comments, the possibility arises of utilizing this regularity for determining and predicting the toxicometric parameters of chemical compounds. First of all, dependence curves for concentration–time, reflecting as they do the toxicodynamics of a substance and the ability of an organism to compensate for its action, permit one to judge the danger of a chemical compound, i.e., the probability of the appearance of harmful effects in man under actual conditions of contact with the agent involved. Indeed, to the extent that the tangent of the angle of incidence of the curve indicates how many times the logarithm of the time of occurrence of the toxic effect increases upon a reduction in the logarithm of concentration to one, a higher absolute value for the tangent indicates a lesser hazard from the substance.

Thus, by utilizing the parameters of concentration–time curves, substances can be classified according to the degree of hazard from them (Fig. 1 and Table 1). It follows that upon reducing the concentration tenfold, the time at which the effect occurs after continuous inhalation of extremely hazardous substances increases only threefold; for highly hazardous ones, 19-fold; for moderately hazardous ones—27-fold; and for those of little hazard, by more than 27 times.

The classification presented describes substances in relation to the danger of chronic intoxication, other conditions being equal, and indicates that the more dangerous a chemical compound is, the lower its threshold of chronic action. In connection with this, upon establishing the maximum allowable con-

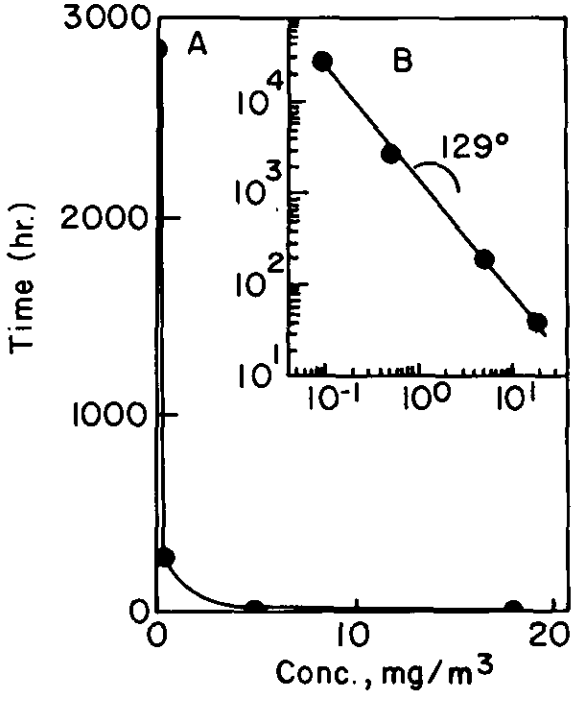

FIGURE 1. Time relationship of the appearance of erythrocytes with Heinz corpuscles in white rats from the aniline concentration in the air during constant inhalation (*A*) normal scale; (*B*) logarithmic scale.

centrations of such a substance for preventing chronic effects, the highest safety coefficients should be used.

To the extent that under actual conditions, the danger of the appearance of acute harmful effects (for example, irritant effects, aggravation of chronic illnesses) rises with a steep rise in pollutant concentrations, there exists the necessity of classifying substances with regard to the danger of the development of acute reactions. In this case, the classification presented above will be the reverse, since upon raising the concentration level ten times, the time of occurrence of an acute effect will be shortened only threefold for the action of Class 1 substances, while it will drop more than 27 times for the action of Class 4 substances. Consequently, in the latter case, even a slight increase in the level of existing concentrations is sufficient for the appearance of acute effects. It is necessary to take this into account in choosing safety coefficients when setting maximum allowable concentrations, specifically for atmospheric pollutants.

In this way, the concentration–time dependence curves, which permit classification of substances according to the degree of danger of development of chronic and acute harmful effects, indicate the necessity of selecting differentiated safety coefficients when establishing the maximum allowable concentrations. This is especially important when the latter are predicted on the basis of short-term experiments. Application of the concentration–time dependence can be recommended as one of the routes for predicting the maximum allowable concentrations for atmospheric pollutants.

The possibility of expressing the dependence mentioned in the form of a straight line on a logarithmic scale grid enables us to propose a method for predicting the threshold of chronic action on the basis of a short-term experiment (up to one month) with four or five concentrations and subsequent extrapolation of the curve to four months, as is shown in Figure 2.

The threshold of chronic action predicted on the basis of study of the concentration–time dependence in a short-term experiment is determined more accurately in theory than when determined in the contemporary setting of chronic experiments eliciting "ineffective" concentrations. In the latter case, the value of the threshold concentration frequently depends on the simple accident of the concentration chosen for the experiment and on the degree of disparity in the concentrations under study. Often chance selection of the concentration influences the likelihood that the safety coefficient selected may shift from the threshold of chronic action to the maximum allowable level.

Of course the question of the selection of the safety coefficients is quite complicated and goes far beyond the framework of animal experiments, becoming interwoven with the problem of extrapolation of the data of this experiment to man. However, with all the complexity of the given problem at the present time, it is evident that the coefficients of

Table 1. Classification of hazard from substances according to parameters of the concentration–time curve.

	Parameters of curve			
Class of hazard	Angle of incidence	Tangent of angle of increase	Decrease in concentration of substance	Increase in time for occurrence of effect
1st: Extremely hazardous	> 155°	< 0.475	10×	≤ 3×
2nd: Highly hazardous	155–137°	0.475–0.950	10×	3-9×
3rd: Moderately hazardous	137–125°	0.950–1.425	10×	9-27×
4th: Slightly hazardous	< 125°	>1.425	10×	>27×

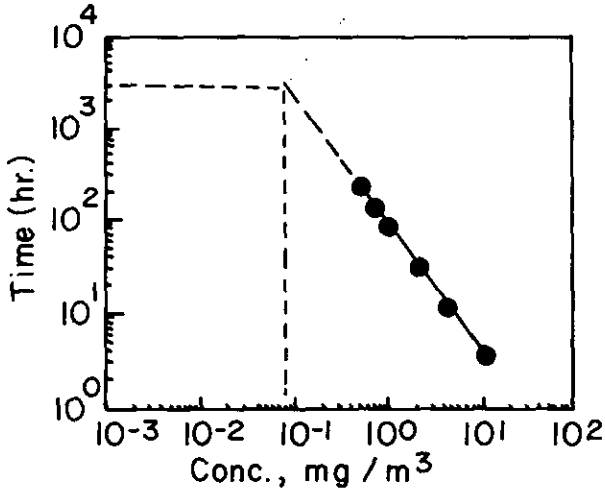

FIGURE 2. Diagram for predicting chronic effect thresholds of harmful substances by extrapolating the concentration–time curve.

safety must be differentiated depending on the class of hazard of the substances being studied.

For the transition to the MAC from the predicted threshold of chronic action, a scale of coefficients of safety has been worked out corresponding to the danger of the substances, determined along parameters of the concentration–time curve.

In determining the scale of safety coefficients, it was advisable to take into consideration not only the hazard of the development of chronic intoxication in line with the reduction in the concentration of the substance, but also the danger of the occurrence of acute harmful effects upon a sharp increase in the level of actual concentrations in the air. Hence, in the first case of safety coefficient directed to preventing chronic poisoning must be greater the more hazardous the substance is, since with the same reduction in concentration such a substance will induce a harmful effect earlier than a less hazardous substance. In the second case, when a sharp rise in concentration is observed and the danger of acute exposure appears, the safety coefficient must be greater the less hazardous the substance is, since with the same increase in concentration as in the hazardous substance, a rapid decline occurs in the time needed for the occurrence of an acute effect.

In connection with the role of safety coefficients noted, a nomogram for determining their values was developed for substances of various classes. The least safety coefficient, equal to five, is established at the boundary of moderately and highly hazardous substances (angle of incidence of the concentration–time dependence curve is equal to 137°). From this value of the coefficient, the coefficient increases 25-fold and more, both in the case of increasing and of decreasing hazard of chronic poisoning.

In order to verify the acceptability of the proposed scale of safety coefficients the following was carried out: a comparison of epidemiological data and levels of MAC in an atmosphere of air for substances that are widely distributed and have been relatively well studied; a comparison of existing proposals for determining safety coefficients in the field of occupational hygiene; and, finally, a comparison of the predicted MAC with the MAC for the same substances in atmospheric air, as determined in a chronic experiment.

As a result of these comparisons, data were obtained confirming the possibility of applying the nomogram developed for coefficients of safety for predicting the MAC of atmospheric pollutants. In addition, as additional data become available, the ways proposed for predicting toxicometric parameters on the basis of the concentration–time dependence will undoubtedly be refined and perfected.

REFERENCES

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