Technical Report

No 22

Classification of Dangerous
Substances and Pesticides in the
European Economic Community
Directives: A Proposed Revision of
Criteria for Inhalation Toxicity

1987

Classification of Dangerous Substances and Pesticides in the European Economic Community Directives: A Proposed Revision of Criteria for Inhalation Toxicity[1]

H.-J. KLIMISCH,* R. BRETZ,† J. E. DOE,‡ AND D. A. PURSER§

*BASF Aktiengesellschaft, Department of Toxicology, 6700 Ludwigshafen, West Germany; †Ciba-Geigy AG, Toxikologie, 4002 Basel, Switzerland; and ‡Imperial Chemical Industries Plc, Central Toxicology Laboratory, Alderley Park, Nr. Macclesfield, Cheshire SK10 4TJ, United Kingdom; and §Hartford, Huntingdon, Cambridgeshire PE18 7PG, United Kingdom

Criteria for the classification of dangerous substances with respect to their inhalation toxicity were originally proposed by the European Economic Community (EEC) on the basis of a 1-hr LC_{50}, as were the similar United Nations (UN) "transport" criteria. Both sets of criteria have since been amended for a 4-hr LC_{50}, but whereas the UN criteria limits have been decreased to compensate for the increased exposure time, the EEC limits have not. This has introduced an anomaly into the EEC classification scheme whereby substances are classified more severely than they were previously. The EEC scheme is now out of line with the UN criteria and other international guidelines and gives a much more stringent toxicity classification for individual substances by inhalation than by the oral route, as well as causing an unjustifiable duplication of animal tests. This anomaly has led to a proposal by the Federal Republic of Germany for revised criteria. This paper examines the scientific basis for the relationship between inhalation exposure duration and toxicity, and for a comparison of the LD_{50} and LC_{50} classifications for individual substances. It is concluded that the proposed German revised classification scheme is more in line with the UN transport criteria and international guidelines and provides a rational basis for a classification scheme for inhalation toxicity. The classification criteria therefore should be harmonized by a revision of the EEC classification limits for inhalation toxicity. © 1987 Academic Press, Inc.

INTRODUCTION

In recent years attempts have been made through a number of international organizations to harmonize national regulations on test methods for the evaluation of the

---

[1] This paper has been drafted by Dr. D. A. Purser on the basis of a document prepared by Dr. H.-J. Klimisch, Dr. R. Bretz, and Dr. J. E. Doe (1984), for the European Discussion Group of Inhalation Toxicologists (EDIT). It is published as ECETOC Technical Report No. 22. All comments should be sent to Dr. Klimisch.

toxicity of dangerous substances and on criteria for their classification. In particular, criteria have been developed and applied to the notification scheme for new substances and two particular risk situations, the handling (supply) and transport of dangerous substances.

The recommendations developed by the different international bodies have undergone a process of gradual update and change, and although they are now fairly well developed and there are great similarities between them, there are still some differences between the different international guidelines. In one particular area, that of limit criteria for inhalation toxicity, an anomaly has occurred in the European Economic Community (EEC) criteria which is highlighted by differences between the EEC recommendations and those of other international guidelines (EEC, 1978, 1979; United Nations (UN), 1977, 1983).

The purpose of this paper is to demonstrate how this anomaly in the EEC classification criteria has developed, how it differs from the recommendations of other international bodies, how it distorts the classification of toxic substances, and how a scientific basis can be established for correcting the anomaly.

The arguments of the paper are presented in three parts:

1. A description of how the guidelines for test methodology and criteria for classification or toxic substances have developed in the EEC and in other international bodies. This shows how by changing from a 1-hr to a 4-hr LC_{50} test without adjusting the limit criteria an anomaly has been introduced into the EEC classification scheme whereby substances are now classified as approximately four times as toxic by inhalation as they were previously, how this is against the spirit of other EEC and international recommendations, and how the anomaly can be corrected.

2. A description of the scientific basis for the relationship between toxicity and duration of exposure and for a valid comparison of the 1- and 4-hr LC_{50}s.

3. A comparison of the toxicity classification of substances by the oral and inhalation routes which shows that under current EEC regulations there is a considerable imbalance between the classification criteria for the two modes of administration. The comparison also shows that the limits are excessively stringent for inhalation, resulting in an overclassification for inhalation toxicity, and shows how the proposed simple change in the criteria eliminates this anomaly.

DEVELOPMENT OF CLASSIFICATION CRITERIA AND TESTING GUIDELINES

Criteria Based on a 1-hr Exposure

a. *United Nations "transport" criteria.* Recommendations for the classification of dangerous goods during transport have been published in various documents by the United Nations Committee of Experts on the Transport of Dangerous Goods. The criteria for defining inhalation toxicity are expressed differently for vapors and for dusts or mists (UN, 1977); see Table 1.

b. *EEC "handling" criteria.* Criteria for the classification of dangerous substances in respect to handling have been under discussion for a long time and numerous

TABLE 1

INHALATION TOXICITY, LC_{50} (1 hr)—UN, 1977

Group	Vapors (ml/m^3, ppm)	Dusts and mists (mg/liter)
I	<50	<0.5
II	50–200	0.5–2
III	200–1000	>2–10

Note. A conversion of the vapor limit from ml/m^3 to mg/liter, assuming an average molecular weight of 240, results in the same values as given for dusts and mists. The limits for liquids having toxic vapors have since been changed to relate toxicity to vapor pressure (UN, 1983).

proposals have been worked out within the European Economic Community on the basis of the council directive of June 27, 1967 (EEC, 1967).

Although there was no explicit specification, it was generally assumed that the criteria were based on 1-hr LC_{50} values, which were customary at that time, and which were specified in another EEC directive proposal for pesticides (EEC, 1975). These criteria for classification on the basis of 1-hr LC_{50} data were also proposed for application to dangerous substances (EEC, 1976). Except for the upper limit of the "harmful" category of 20 mg/liter, these criteria were the same as those recommended for transport by the United Nations on the basis of the 1-hr LC_{50}s as follows:

TABLE 2

INHALATION TOXICITY, LC_{50} (1 hr)—PROPOSAL EEC 1976

Group	All substances (mg/liter)
Very toxic	<0.5
Toxic	0.5–2
Harmful	>2–20

Adaptation of Criteria to 4-hr Exposure

In accordance with the continuing development of toxicology over the past few years, a 4-hr LC_{50} test is now being recommended in place of a 1-hr LC_{50} because prolonging the exposure time from 1 to 4 hr produces more reliable results. This is recognized in the major international testing guidelines, in the OECD guidelines (OECD, 1981), in the EPA guidelines (EPA, 1982), and also in the EEC testing guidelines (EEC, 1984).

A second difficulty with the original testing guidelines and testing criteria has been the upper concentration limit of 20 mg/liter, which is so high that often it is not technically possible to achieve such a concentration of respirable material in inhalation chambers. This is especially difficult with aerosol studies, where secondary effects such as agglomeration of particles, inhomogeneity of the test atmosphere, and sampling errors make it difficult to achieve such high concentrations or to characterize them by reliably measurable data. Also, even an inert dust may cause the animals to die of suffocation at concentrations approaching 20 mg/liter, because the material

may block the nostrils. These high concentrations are unrealistic both in terms of hazard situations and in terms of ability to assess the toxicity of materials.

Fortunately, increasing the exposure period from 1 to 4 hr presented the opportunity to reduce the concentration limits while still achieving the delivery of approximately the same dose to the animals. This was achieved by dividing the limit concentration of 20 mg/liter by 4, following a basic principle of inhalation toxicology, according to which the effect of a substance is a function of both the concentration in the inhaled air and the duration of exposure. The longer the exposure the more severe is the effect, a relationship known as Haber's rule (Flury, 1921; Haber, 1924).

This fact was appreciated internationally and was taken into account in the international testing guidelines (OECD, 1981; EPA, 1982) and in the EEC test methods (EEC, 1984). A limit test for studies on aerosols at a concentration of 5 mg/liter is recommended by all these guidelines and proposed test methods, and as the exposure time was prolonged from 1 to 4 hr, this concentration limit was obtained on the basis of Haber's rule by dividing the 20 mg/liter limit by 4.

Adaptation of Classification Criteria

a. United Nations transport criteria. Within the framework of general efforts to reduce the number of animal experiments and to avoid unnecessary repetitions these time and concentration factors were recognized by the United Nations, and a change in the United Nations Recommendations on the Transport of Dangerous Goods has been accepted (UN, 1983). According to these Recommendations, values from 4-hr LC_{50} tests can be employed for classifying a substance after the equivalent 1-hr LC_{50}'s are estimated by multiplying the 4-hr LC_{50} values obtained by a factor appropriate to the prolonged exposure time (a factor of 4 for dusts and mists, and a factor of 2 for vapors). The estimated 1-hr LC_{50} value is then used to classify the material.

b. Current EEC handling regulations. In line with the United Nations transport criteria, the OECD (1981) and EPA (1982) testing guidelines, and its own proposed test methods (EEC, 1984), the EEC classification criteria for pesticides and dangerous substances with respect to handling have been modified to include a prolongation of the exposure time to 4 hr. However, unlike the above authorities, and in obvious contrast to the general rule in inhalation toxicology that the biological effect is a function of the concentration and the exposure time according to Haber's rule, the classification criteria were retained without adaptation to the fact that the exposure times had been prolonged fourfold, so that there are now considerable differences between the UN and EEC criteria (see Table 3). The basic reasoning, and scientific judgment, behind this decision not to adjust the limits of the classifications to the prolongation of the exposure time is not known, and this has led to general uncertainty and inconsistencies as follows:

1. The criteria are in conflict with the limit test accepted by the EEC, which puts forth 5 mg/liter as the highest concentration to be tested during 4 hr of exposure, while the criteria state that up to 20 mg/liter is to be considered harmful.

2. Observations using 4-hr exposures have generally confirmed, especially with the inhalation of dusts, that larger amounts are taken up by animals and accumulated when the inhalation time is prolonged. Hence, the "dose" (the amount taken up by

TABLE 3

INHALATION TOXICITY LC_{50} (4 hr)

Group	United Nations (1983) (4-hr equivalent) Dusts and mists (mg/liter)	78/631 EEC 79/831 EEC All substances (mg/liter)	
I	<0.125	Very toxic	<0.5
II	0.125–0.5	Toxic	0.5–2
III	0.5–2.5	Harmful	2–20

the lung) really is a function of the time and the concentration. Also the limits do not take into account published results of investigations comparing 1- and 4-h LC_{50} values (Sachsse et al., 1974) and those described in this paper.

3. Experimental data presented in this paper indicate a considerable imbalance between the classification criteria for oral and inhalation exposures. If the classification criteria for oral and inhalation toxicity were equally stringent most substances should obtain a similar toxicity rating via either route of administration. This is because the majority of substances exert their toxicity via systemic effects and it is reasonable to expect similar toxicity induced by either the oral or the inhalation route. Obviously there will be exceptions to this general rule due to uptake and absorption differences between the two routes and local toxicity in either the lung or the digestive tract. In practice the data show that the classification limits for inhalation are much more stringent than those for oral administration and that chemicals are frequently "overclassified" on the basis of the current EEC classification limits for inhalation toxicity (Table 6) (Bretz and Hess, 1984). In addition, many materials which have been used safely in the past will be unnecessarily reclassified as "more toxic." The difference in the upper criteria (5 mg/liter versus 20 mg/liter) will lead to the use of additional laboratory animals merely to satisfy the differences in regulations with little or no benefit in practical safety.

4. In order to fulfill the different UN and EEC criteria some duplication of animal testing is required, although no scientific justification for these different requirements has been put forward.

Proposals for an Adaptation

The consequences of the present situation are unsatisfactory because in practice, careful scientific assessment of inhalation toxicity is replaced by a superficial general assessment that "everything is toxic (or harmful) by inhalation." These problems have been discussed at a meeting in the German Ministry of Youth, Family, and Health (Bonn, 1978), and a document was compiled on the basis of the scientific arguments of reports by experts (Klimisch, 1979) and results of acute inhalation toxicology investigations (Kunde, 1979). This document was submitted to the Scientific Advisory Committee of the EEC (Kunde, 1980). A proposal (Federal Republic of Germany, 1980) was made that these problems should be discussed and the relevant

TABLE 4

Inhalation Toxicity LC_{50} (4 hr)

Group		Current 78/631, 79/831 EEC limits (mg/liter)	German proposed limits (mg/liter)
I	Very toxic	<0.5	<0.1
II	Toxic	0.5–2.0	0.1–0.5
III	Harmful	2.0–20	0.5–5.0

paragraphs (Annex VI, A, (a) of EEC 79/831 and Article 3(1)(b) of EEC 78/631) should be modified to show revised classification limits for the 4-h inhalation LC_{50}, which are shown in Table 4.

THE RELATIONSHIP BETWEEN CONCENTRATION INHALED, DURATION OF EXPOSURE, AND TOXICITY

If the increase in the duration of the LC_{50} test from 1 to 4 hr is intended simply to provide a more reliable estimate of toxicity rather than to impose more stringent classification criteria for inhalation hazard, it is essential to examine the relationship between exposure concentration and duration to determine the consequences. It has long been an established principle of inhalation toxicology that toxicity depends on both the concentration of a toxic substance to which an animal is exposed and the time for which it is exposed. Indeed this principle is the basis of the inhalation hazard test for volatile chemicals proposed in the OECD guidelines (1981), whereby the toxicity of different chemicals is compared on the basis of time to lethality for a constant concentration (LT_{50}). Obviously if a given concentration is inhaled for 4 hr it is likely that this will lead to the intake of a much greater "dose" than would a 1-hr exposure. In its simplest form, where the inhaled substance accumulates in the body and is not rapidly destroyed or excreted, the dose accumulated is directly proportional to the concentration, c, and the exposure time, t, and uptake is linear. This concept was first formulated empirically by Haber (1924) and by Flury (1921) and Flury and Zernik (1931) as

$$W = c \times t, \tag{1}$$

where W is a constant dose specific for any given effect. In this case the effect is the death of 50% of the animals and $W = LCt_{50}$ in mg·min/liter.

This relationship will hold true for any substance for which the half-life for detoxification or excretion is long with respect to the exposure duration, and it is particularly applicable to many dusts and liquid aerosols (as recognized in the 1983 UN criteria), and also to many substances where the primary target organ is the lung. Thus, for example, the pulmonary irritant carbonyl fluoride has a 1-hr LC_{50} of 0.990 mg/liter which is exactly four times that of the 4-hr LC_{50} of 0.248 mg/liter (ACGIH, 1980):

for 1 hr $W = 0.990 \times 60 = 59.4$ mg·min/liter

for 4 hr $W = 0.248 \times 240 = 59.5$ mg·min/liter

so that W is the same for both exposure times.

This rule has been used as a guide in inhalation toxicology for many years, but there is an obvious exception in that some substances may be detoxified or excreted as fast as they are inhaled so that accumulation does not occur until a certain threshold concentration is inhaled when the rate of uptake exceeds the maximum rate of removal. Accumulation then proceeds at a rate dependent upon the difference between the inhaled concentration and the threshold concentration (the rate of uptake and the constant rate of removal), as described by Flury and Zernik (1931):

$$W = (c - a) \times t, \tag{2}$$

where a is the threshold concentration. This relationship approaches Haber's rule (eq. (1)) when the atmosphere concentration c is large compared to the threshold concentration a.

A third situation may occur with certain volatile substances (such as carbon monoxide) which are both taken up and excreted via the lungs. In this case the rate of uptake depends upon the difference between the concentration inhaled and that in the body, giving a curved uptake line with a gradually decreasing rate of uptake, so that

$$W = c(1 - e^{-tk}), \tag{3}$$

which is the basis for the Coburn–Forster–Kane equation (Coburn *et al.*, 1965; Peterson and Stewart, 1975). This also approaches Haber's rule (Eq. (1)) when the concentration c is high with respect to the body concentration required to cause death and t is relatively short. This then gives an almost linear uptake line.

In practice these complicating factors mean that we can expect a few exceptions to Haber's rule, but whether the relationship is likely to be affected significantly for periods of up to 4 hr can be determined only be experimentation. Apart from the work of Haber and Flury, the relationship between the 1- and 4-hr LC_{50}'s has been investigated by Sachsse *et al.* (1974) and in a recent literature review by Doe and Milburn (1983), who examined the relationships between concentration and time for 33 volatile chemicals. For substances obeying Haber's rule, plots of log LC_{50} versus log exposure time are linear with a slope of -1:

$$\text{from Haber} \quad c = w/t$$

therefore

$$\log c = \log w - t.$$

Doe and Milburn found that for some chemicals, plots of log c versus log t gave a cluster of slopes around -1, as predicted by Haber's rule, while others gave curves which deviated from the theoretical slope of -1 to a varying extent. For some chemicals the slopes tended to cluster around a value of approximately 0.5, and the relationship between concentration and time is better described by

$$W = c \times t^{0.5}.$$

These represent compounds with appreciable rates of detoxification or excretion over the time in question.

These equations can be used to extrapolate between the two time periods in question, i.e., 1- or 4-hr LC_{50}'s. When extrapolating from 4 to 1 hr the equation $W = c \times t^{0.5}$ predicts lower LC_{50} values than does Haber's rule, i.e., it predicts severer toxic-

ity. On the other hand, Haber's rule predicts a lower LC_{50}, and therefore severer toxicity for any particular chemical when going from a 1- to a 4-hr LC_{50}. This principle was applied by the UN (1983) in deciding the conversion factor of 2 to allow classification of materials on the basis of a 1-hr LC_{50} using 4-hr LC_{50} data. To classify on the basis of 4-hr LC_{50} data by the EEC, the appropriate course of action is to extrapolate the previous 1-hr criteria to the 4-hr criteria using a factor of 4 as derived from Haber's law ($w = c \times t$), although this may mean that some substances with appreciable rates of excretion or detoxification will be classified as less toxic than they would under the 1-hr criteria.

Conclusions

1. There is thus ample evidence that in almost all cases toxicity increases greatly when the exposure time is lengthened, so that increasing the exposure time from 1 to 4 hr without changing the criteria definitely distorts the classification system.

2. There is also good evidence that for the majority of dusts and liquid aerosols, and for many vapors, it can be expected that Haber's rule will hold broadly true for periods of up to 4 hr, so that the 4-hr LC_{50} will be approximately one-quarter that of the 1-hr LC_{50}.

3. The German proposal for modified criteria therefore better preserves the original classification.

THE CORRELATION BETWEEN ORAL LD_{50} AND INHALATION LC_{50} DATA, AND BETWEEN ORAL AND INHALATION CLASSIFICATION LIMITS

Another way of considering the inhalation LC_{50} hazard criteria is to compare them with those applied to the oral LD_{50}. It has been observed (Kunde, 1980; Federal Republic of Germany, 1980) that the application of the current EEC classification limits leads to a much more stringent classification of substances on the basis of inhalation toxicity than it does on the basis of oral toxicity. However, the application of the proposed German limits gives a more balanced classification.

Since it is likely that for the majority of substances toxicity results from systemic effects, it is reasonable to expect a common toxicity induced by either route of application and that there will be a correlation between oral and inhalation toxicity for many individual substances. If such a correlation does exist it would be appropriate for a toxicity classification system to use approximately equally stringent criteria for both routes.

Obviously there will be exceptions to this general rule for some substances due to differences in uptake and absorption by the two routes and also in situations where either the respiratory tract or digestive system are the primary target organs for toxicity. This concept of a common toxicity by the oral and inhalation routes would be supported by the demonstration of a statistical relationship between oral LD_{50} values and inhalation LC_{50} values. However, it could never serve to forecast the inhalation toxicity of any individual substance and could not replace experimental inhalation testing. Such a relationship would nevertheless enable judgments to be made on the

relative stringency of oral and inhalation criteria, for if such a relationship did exist it would be reasonable to expect the majority of substances to be classified in the same category by both routes, although there would of course be a number of exceptions.

This section of the paper summarizes an investigation (Bretz and Hess, 1984) which

1. Demonstrates such a correlation by comparing the oral LD_{50} and inhalation 4-hr LC_{50} for 265 substances.

2. Uses two statistical methods to derive possible classification limits for the inhalation LC_{50} from the existing oral LD_{50} classification system:

    (a) based directly on the correlation between the oral and inhalation toxicities of individual substances, or

    (b) based on the statistical distribution of oral LD_{50} and inhalation LC_{50} data.

and compares these classification limits with the existing EEC limits and the proposed German limits.

3. Examines the consequences in terms of hazard classification of applying the existing EEC inhalation limits and the German proposed limits to the LD_{50}s and 4-hr LC_{50}s for 505 substances (including the original 265 substances).

Correlation between Oral LD_{50} and Inhalation 4-hr LC_{50} and Classification Limits Based on Oral Toxicity Criteria

Data pairs from 265 chemicals with numerically defines LC_{50}'s and LD_{50}'s were compared by a least-squares regression of log LC_{50} on log LD_{50}. The results (Fig. 1) show a correlation which follows the equation

$$\log LC_{50} = -1.868 + 0.746 \times \log LD_{50}$$

with a correlation coefficient of 0.719. This supports the original hypothesis of a relationship between oral and inhalation toxicity. Naturally there is scatter on both sides, and the outliers presumably represent cases where route-dependent differences in bioavailability or target organ specificity occur. The regression equation derived from this relationship can then be used to derive classification limits for LC_{50}'s based on the existing LD_{50} scheme as shown in Table 5. The relationship, of course, cannot be used to predict the toxicity of any specific compound, being merely an overall trend, and cannot replace adequate toxicological evaluation by the appropriate route or routes.

Classification Limits Based on Oral and Inhalation Toxicity Distribution Functions

The demonstration that there is a correlation between individual LC_{50}'s and LD_{50}'s opens up the possibility of another basis for the determination of inhalation toxicity limits. A completely balanced system for oral and inhalation toxicity would result in equal percentages of entries in any given toxicity class by either route, with perhaps a few substances classified more severely by inhalation due to local pulmonary toxicity having severe consequences. In order to derive such a system it is necessary to deter-
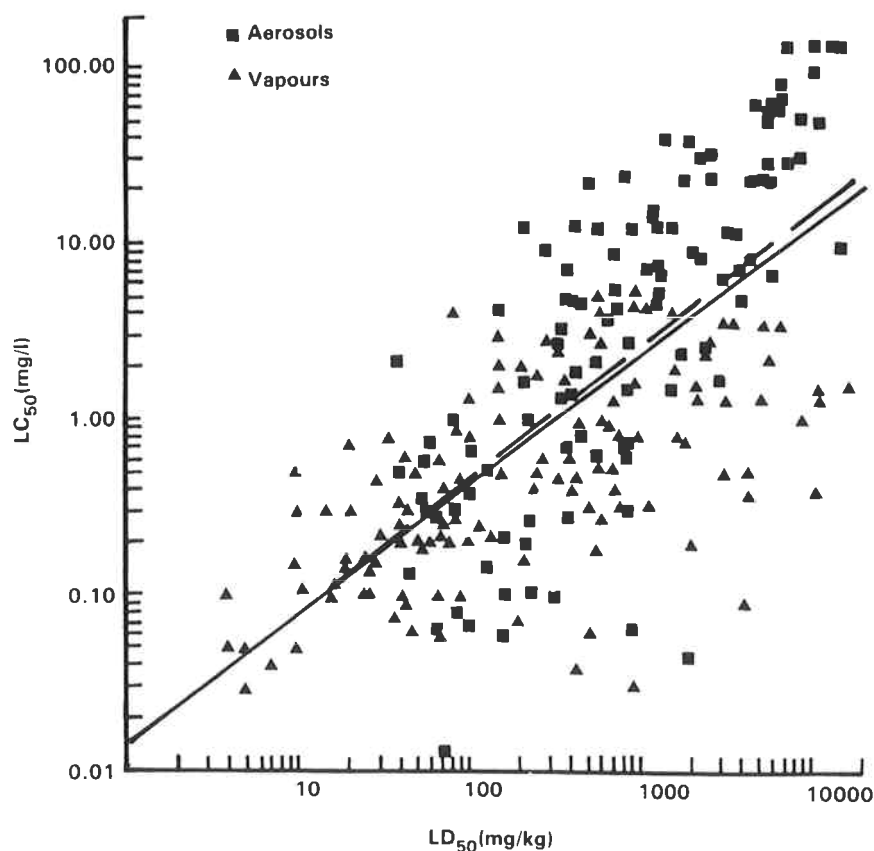
KLIMISCH ET AL.

FIG. 1. Double-logarithmic correlation of inhalation LC_{50} and oral LD_{50}. Solid line, least-squares regression; broken line, nonparametric regression.

mine the frequency distributions of oral LD_{50}'s and inhalation LC_{50}'s. When the LD_{50}'s and LC_{50}'s of 505 substances were plotted as histograms, both distributions were found to be log-normal. The total population under the bell shaped LD_{50} curve was split into class segments corresponding to the existing EEC limits, and the LC_{50} curve was split into corresponding class segments with the same areas as those under the oral curve, so that the proportion of substances in each class was equal for both

TABLE 5

COMPARISON OF TOXICITY CLASS LIMITS DERIVED FROM REGRESSION AND DISTRIBUTION ANALYSES WITH EXISTING EEC LIMITS AND GERMAN PROPOSED LIMITS

Method of estimation	Very toxic	Toxic	Harmful
	Oral LD_{50} (mg/kg)		
	25	200	2000
	Inhalation LC_{50} (mg/liter)		
Least-squares regression	0.150	0.706	3.93
Frequency distribution	0.061	0.375	2.81
Existing EEC regulations	0.500	2.000	20.00
German proposal	0.100	0.500	5.00

TABLE 6

PERCENTAGE DISTRIBUTION AMONG TOXICITY CLASSES OF LD_{50}s AND LC_{50}s FOR 505 SUBSTANCES

	Very toxic	Toxic	Harmful	< Harmful
Oral LD_{50}	5.0	19.6	37.7	37.7
EEC LC_{50}	31.5	31.5	30.5	5.3
German LC_{50}	8.4	23.1	51.8	16.7

routes of application. This then gave a new classification for LC_{50} limits derived from the well-established oral values (Table 5) which, in general, support the proposed revision of the criteria.

Comparison of Limit Classifications and Distribution of LD_{50}'s and LC_{50}'s According to the Existing EEC and Proposed German Criteria

The two methods for deriving inhalation toxicity classification limits from oral toxicity limits, one based on the regression of 265 individual LD_{50}–LC_{50} pairs and the other based on the independent frequency distributions of 505 LD_{50}'s and LC_{50}'s, can be compared with the existing EEC limits and proposed German limits in Table 5. This shows that for each of the three toxicity limits the EEC criteria are three to eight times more stringent than those derived from oral LD_{50} data. The limit criteria of the German revised classification scheme are much closer to the LD_{50}-derived limits in all classes, but are still somewhat more stringent than those of the balanced system derived from frequency distributions, in the rating of inhalation toxicity.

The consequences of applying the existing EEC LC_{50} limit criteria and those of the German revised classification to the 505 substances with respect to oral and inhalation toxicity classes are shown in Tables 6 and 7. Table 6 shows that the EEC LC_{50} classification scheme gives a clear bias toward more stringent classification for the inhalation route, and Table 7 shows that 66% of individual substances are classified as one or more classes more toxic by inhalation than they are by the oral route, while only 31% are in the same category and 3% are classed as less toxic by inhalation. Also, with the current EEC LD_{50} and LC_{50} limits, 62% of substances are classified into the very toxic or toxic classes solely on the basis of their inhalation LC_{50}, whereas their oral LD_{50}'s warrant a classification as harmful or even nontoxic (Fig. 2). In practice, this results in the reclassification of many chemicals tested before the change from the 1- to the 4-hr LC_{50}.

The German revised classification scheme, however, gives a distribution which provides many more similar ratings for individual substances. Thus 45% are classified identically, 33% one class more toxic by inhalation, and 15% one class less toxic. Some 92% of the 505 LD_{50}/LC_{50} pairs are thus found in identical or adjacent classes, although 7% are still classed as two or more classes more toxic by inhalation than by the oral route (which would be expected given the severe consequences of local pulmonary damage).

These findings are consistent with the large set of toxicity data examined and further strengthen the case put forward in the first two sections of this paper for the adoption of the German revised classification scheme.

TABLE 7

CORRELATION OF ORAL AND INHALATION TOXICITY CLASSES ACCORDING TO CURRENT EEC
REGULATIONS AND THE GERMAN PROPOSAL

	Toxicity class correlation				
	2–3 classes more severe	1 class more severe	Identical	1 class less severe	2–3 classes less severe
EEC	26	40	31	3	<0.5
German	7	32	45	15	1

Note. The table shows the toxicity classification of substances by inhalation relative to their oral classifi-
cation, expressed as percentages.

CONCLUSIONS

1. By changing the basis of the handling criteria for inhalation toxicity from a
1-hr to a 4-hr LC_{50} without adjusting the classification limits, the EEC has increased
the stringency of the toxicity classification by approximately a factor of 4.

2. No intention to increase the stringency for inhalation toxicity has been stated
by the EEC, and the current criteria are out of line with respect to the UN transport
criteria and international testing guidelines, including the proposed EEC guidelines
as well as those of the EPA and OECD. Furthermore, the limits will result in the
reclassification of many existing substances and unnecessary restrictions on the use
of new materials, as well as requiring the unnecessary use of additional laboratory
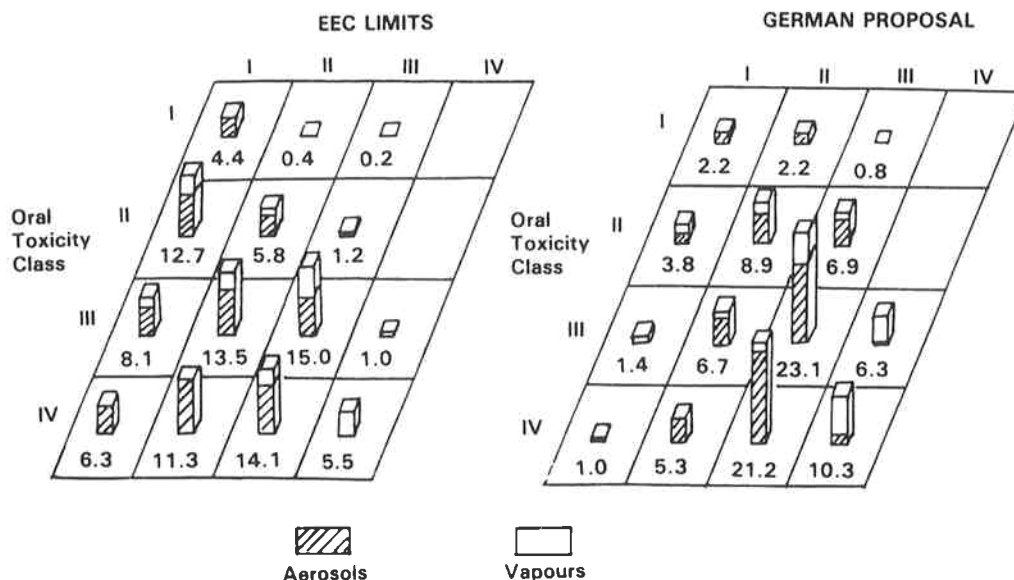animals.

FIG. 2. Oral and inhalation toxicity class correlation (percentage). Relative frequency of oral and inhala-
tion toxicity class combinations, according to the current EEC regulations (left) and the proposed German
classification (right). Under the current EEC regulations many substances are classified as more toxic by
inhalation than they are by the oral route, while under the proposed German classification scheme most
occur in identical or adjacent classes. Toxicity classes: I = very toxic; II = toxic; III = harmful; IV
= practically nontoxic.

3. The proposed German revised classification scheme for 4-hr inhalation LC_{50} limits redresses the situation by providing a classification scheme which is in line with the UN transport criteria and international guidelines, and which provides an adjustment in line with the scientific principles and experience of inhalation toxicology.

4. The scientific data presented in this paper provide support for the German proposal to revise the criteria in order to allow for the increased LC_{50} exposure time.

ACKNOWLEDGMENTS

REFERENCES

ACGIH (1980). *Documentation of the Threshold Limit Values for Substances in Workroom Air.*

Bonn (1978). Meeting in the "Bundersministerium fur Jugend, Familie und Gesundheit," Germany, 20 December 1978.

BRETZ, R., AND HESS, R. (1984). Acute oral and inhalation toxicity: A correlation of experimental results. In *Problems of Inhalatory Toxicity Studies* (P. Grosdanoff, R. Bass, U. Hackenberg, D. Henschler, D. Muller, and H-J. Klimisch, eds.), pp. 39–56. MMV Medizin Verlag, Munich.

COBURN, R. F., FORSTER, R. E., AND KANE, P. B. (1965). Considerations of the physiological variables that determine the blood carboxyhaemoglobin concentration in man. *J. Clin. Invest.* **44**, 1899–1910.

DOE, J. E., AND MILBURN, G. M. (1983). The relationship between exposure concentration, duration of exposure and inhalation LC_{50} values. *Human Toxicol.* **2**, 564.

EEC (1967). 67/548: Council Directive of 27 June 1967 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities,* No. 196, 16.08.67.

EEC (1975). Proposal for a Council Directive on the approximation of the laws of the Member States relating to the classification, packaging and labelling of pesticides, submitted by the Commission of the Council on 31 December 1974. *Official Journal of the European Communities,* No. C 40, 20.02.75.

EEC (1976). Proposal for a Council Directive on the sixth modification of the laws of Member States relating to the classification, packaging and labelling of dangerous substances, submitted by the Commission to the Council on 21 September 1976. *Official Journal of the European Communities,* No. C 260, 05.11.76.

EEC (1978). 78/631 EEC: Council Directive of 26 June 1978 on the approximation of the law of Member States relating to the classification, packaging and labelling of dangerous preparations (pesticides). *Official Journal of the European Communities,* No. L 206, 29.07.78.

EEC (1979). 79/831 EEC: Directive of 18 September 1979 amending for the sixth time Directive 67/548 EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities,* No. L 259, 15.10.79.

EEC (1984). EEC Directive 79/831, Annex V. *Official Journal of the European Communities,* No. L 251, 19.9.84.

EPA (1982). *Toxic substances: Health effects,* Guidelines Report No. EPA 560/6-82-001.

Federal Republic of Germany (1980). *Document CSTE/79/30/V/E/1.* Commission of the European Communities.

FLURY, F. (1921). Uber kampfgasvergiftungen. Uber reizgase. *Z. Gesamte Exp Medizin* **13**, 1.

FLURY, F., AND ZERNIK, F. (1931). *Schaedliche Gase, Daempfe, Nebel, Rauch-und Staubarten.* Springer-Verlag, Berlin, 1931/Nachdruck, 1969.

HABER, F. (1924). *Funf vortrage aus den jaren 1920–1923.* Springer-Verlag, Berlin.

KLIMISCH, H.-J. (February 1979). *Discussion document: Toxicological basis for establishing the exposure time in LC_{50} determinations and the limit values for classification via LC_{50}: limit values for classification: criteria for the determination of 4-hour LC_{50} determinations.*

KUNDE, M. (1979). *Acute toxicity of pesticides.* Bundesgesundheitsamt, Berlin, February 5, 1979.

KUNDE, M. (1980). *Festlegung von grenzkonzentrationen zur klassifizierung gefaehrlicher stoffe und zubereitungen nach deren akuter inhalationstoxizitat.* Presented to the Scientific Advisory Committee, Toxicity Section, Health and Safety Directorate of the Commission of the European Committees, Brussels, July 7, 1980.

OECD (1981). *Guidelines for testing of chemicals, Section 4: Health effects, Method 403.* Organization for Economic Cooperation and Development (OECD), Paris.

PETERSON, J. E., AND STEWART, R. D. (1975). Predicting the carboxyhaemoglobin levels resulting from carbon monoxide exposures. *J. Appl. Physiol.* **39,** 633–638.

SACHSSE, K., ULLMANN, L., VOSS, G., AND HESS, R. (1974). Measurement of inhalation toxicity of aerosols in small laboratory animals. In *Experimental Model Systems in Toxicology and Their Significance in man: Proceedings of the European Society for the Study of Drug Toxicity,* Vol. 15, pp. 239–251. Excerpta Medica, Amsterdam.

UN (1977). *Transport of Dangerous Goods,* ST/SG/AC 10/1 Rev. 1, pp. 159–166. United Nations, New York.

UN (1983). *Report of the Committee of Experts on its twelfth Session,* December 6–15, 1982; ST/SG/AC 10/8, January 24, 1983. Addendum 2, p. 9.