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CONSIDERATIONS REGARDING THE EXTRAPOLATION OF BIOLOGICAL DATA IN DERIVING OCCUPATIONAL EXPOSURE LIMITS

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A. SUMMARY

Data from studies on animals and observations on humans are used to derive health-based limits as a first step in establishing occupational exposure limits for airborne substances. It is realised that for many substances which have been in use for quite some time the available toxicological data is limited. Therefore, in extrapolating animal data for this purpose proposals have been made to use simple, generalised mathematical schemes for deriving the safety factors applied to such data. This situation, however, is not improved by the use of such schemes. The best mathematics does not make poor data good, and does not compensate for the lack of information. In fact, in making this derivation, numerous differences between human and animal physiology and toxicological response, and in the conditions of exposure, should be taken into account. The principles underlying this are discussed.

It is concluded that the use of generalised mathematical schemes for deriving safety factors is to be deprecated because they cannot accomodate the wide variations in animal and human response and the variable quality and quantity of much of the data available. There is no alternative to the use of expert scientific judgement in this matter, on a case by case basis.

This document is intended for the consideration of those involved in the use of biological data in developing and assessing occupational hygiene standards.

B. INTRODUCTION

Limits for occupational exposure to airborne substances are set to safeguard workers from damage to their health as the result of short- or long-term exposure to certain chemicals and substances at the workplace. Well-known examples of such limits are the Maximum Allowable Concentration (MAC), Maximum Accepted Concentration (MAC), Maximale Arbeitsplatz Konzentration (MAK), Threshold Limit Value (TLV) and Occupational Exposure Limits (OEL).

Exposure limits such as TLVs in the USA and MAK values in Germany enable the establishment of "conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect" (ACGIH," Threshold Limit Values", 1980, page 2), or the "maximum permissible concentration of a chemical compound present in the air within a working area (as gas, vapour, or particulate matter) which, according to current knowledge, generally does not impair the health of the employee nor cause undue annoyance"(English edition of "Maximale Arbeitsplatzkonzentrationen", Deutsche Forschungsgemeinschaft, 1982, p.5).

"Because of wide variation in individual susceptibility, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness" (ACGIH, as above). Thus, as is true for all situations in life, it may not be possible to protect all workers from all risks for all of the time.

The establishment of an occupational exposure limit is a two-step process, described by the WHO (1981) as follows : "The first step is the development of recommended health-based exposure limits derived from data on exposure-effect and exposure-response relationships. The second step is the translation of these health-based limits into operational limits (or standards) by the responsible authorities. In reaching a decision on these operational limits, policy-makers may have to take a variety of factors into consideration, eg. the views of governments, employers, and workers and the social, cultural, economic, and technological background." This present report deals essentially with the first step in the above process, ie. the

extrapolation of biological data in developing a proposed health-based limit. This is a task for scientific experts.

Over recent years proposals have been made to use generalised mathematical models for deriving health-based limits. The authors of this report believe that such models are open to serious criticism, discuss the matter in some detail, and propose that a case by case approach is necessary. Carcinogenic effects are excluded from this discussion because there is no generally-accepted, simple method for arriving at exposure limits for carcinogens; see ECETOC (1982).

The ultimate derivation of health-based limits for exposure to airborne substances involves the validation and extrapolation of physiological and toxicological data on humans and/or animals. In this, a distinction should be made between effects which are merely an indication of exposure and effects which indicate a potential hazard to health. A decision is required as to whether a numerical safety factor has to be applied and what its value should be. Differences in toxicokinetics (absorption, distribution, biotransformation and elimination) and toxicodynamics (mode of action) between species, and between individuals within one species, can lead to considerable differences in overall response. It should also be taken into account that there are usually important differences in the conditions of exposure between the experimental animal and the worker at the workplace. Thus the considerations involved in choosing a safety factor will differ from substance to substance, such that no generalised mathematical scheme can be applied.

One example of a generalised scheme for deriving safety factors is that tentatively proposed by Zielhuis and van der Kreek (1979-a and -b). Their scheme is limited to non-carcinogenic, systemic effects and thus the authors exclude consideration of carcinogenicity, and topical effects on the skin, eye and mucous membrane, because they are not amenable to this approach. However, topical contact with gaseous chemicals present in workplace air (eg.chlorine, phosgene and oxides of nitrogen) is important, and should be considered. Such contact is not uncommon and can cause irritation, followed by repair "per secundam intentionem" resulting in chronic injury to the lungs.

Zielhuis and van der Kreek were well aware of the dangers of over-simplification in generalising about safety factors, and indeed stated that "The approach proposed certainly should not be regarded as a definite sliding rule, to be applied on a routine basis. One always has to make a specific qualitative and quantitative decision for each agent, taking into account all available data on dose-effect relationships, types of effects examined and observed, metabolism, etc. The approach presented will only serve as a guide for thinking. In each specific proposal for a permissible level, the way of reasoning followed in extrapolation from animal to man should be presented explicitly". This is a sensible statement of the procedure that should be followed by experts in deriving safety factors and recommending health-based limits, and it would seem incompatible with the adoption of generalised mathematical formulae of the type that is nevertheless put forward for discussion.

C. PURPOSE AND SCOPE OF HEALTH-BASED LIMITS FOR AIRBORNE SUBSTANCES AT THE WORKPLACE

In considering the derivation of health-based limits for workplace exposure it is necessary to bear in mind the purpose, scope and other aspects of such limits.

1. The purpose of health-based limits is to provide a preliminary basis for establishing occupational exposure limits.

2. Health-based limits do not represent a sharp dividing-line between safe and unsafe conditions.

3. Health-based limits have to be reviewed and amended as further information accumulates and experience is gained.

4. In deriving health-based limits, valid data on humans takes preference over data from valid animal experiments, but the latter are nevertheless always taken into consideration.

5. When there are no valid data on humans, health-based limits have to be derived by extrapolation of the data available from animal experiments.

D. SOME PRINCIPLES UNDERLYING THE DERIVATION OF HEALTH-BASED LIMITS

In this chapter the derivation of health-based limits, including the choice of safety factors, is discussed in general. A safety factor is a number by which a no-adverse-effect level demonstrated in studies on an animal model, or in investigations on humans, must be divided to arrive at a proposal for a health-based limit.

1. Use of Human Data.

Data on humans can be obtained from observations on volunteers, industrial experience or epidemiological studies. Such data are particularly valuable if they lead to the establishment of a dose-effect relationship.

1.1. Observations on volunteers.

Such observations are available only on a limited number of substances. They are made with short-term exposures at low dose levels under well-controlled conditions. They involve the determination of specific effects under well-defined conditions of exposure to a specific substance, and may be of considerable help in choosing safety factors and setting ceiling and time-weighted-average exposure limits.

1.2. Industrial experience.

Periodical medical examination and/or biological monitoring of exposed workers give information which is particularly useful for: i) assessing the adequacy of exposure limits ; ii) interpreting the relevance to man of experimental data on animals; and iii) detecting or excluding the occurrence of early effects in man.
In using the results from such surveillance the main limitation is that, as regards long-term effects, the relevant atmospheric concentrations in the past may not have been adequately measured and therefore have to be estimated.

1.3. Epidemiological studies.

Adequate epidemiological data will be decisive for setting a health-based limit. In deciding whether, and how, such data can be so used the following need to be considered.

a) Are the results of the study valid in relating cause and effect ? In assessing this, the results of the study should be examined for
   - consistency (an association seen in several studies is more credible than one seen only in a single study)
   - strength of the association
   - specificity of effects and sensitivity of the method
   - dose-effect relationships
   - temporal differences between the exposure and the manifestation of the effect
   - statistical significance
   - factors which interfere with the interpretation of the results, e.g. the causitive agent may arise from different sources; a specific disease in man may have different causes; there may be additional exposure to other chemicals.

b) Can the results be extrapolated from the group studied to the population to be protected ? In this respect, ethnic differences, medical history, age, sex and life-style (diet, alcohol and/or tobacco consumption, hobbies, social behaviour, etc.) may play a role.

Finally, in deciding upon any safety factor, the above information has to be considered together with :

- the design of the epidemiological study, and the number and relevance of the subjects being studied (volunteers, workers, general population, children, patients with a particular disease). An excellent study on fewer people gives more confidence than a superficial study on more people but in which clinical knowledge and experience is disregarded;

- the type and seriousness of the early or low-dose effect, and of the subsequent effects occurring when the dose or concentration rises;

- the warning properties of both the chemical itself (sensory thresholds and sensations) and the effect it exerts.

Valid epidemiological results, taken together with observations on volunteers and data from periodical medical examination and biological surveillance, if available, can then be used to derive the health-based limit.

2. Use of Animal Data.

In deriving health-based limits for humans by the extrapolation of animal data, the data have to be correctly interpreted and safety factors usually need to be applied. The determination of the safety factor depends on the considerations discussed below.

2.1. Adequacy of the animal model.

Although there are well-known differences and variations in toxicokinetics and toxicodynamics between species, the results from experiments on animals can usually be interpreted to give a reasonable idea of the effects in man. It is, nevertheless, always important to consider the adequacy of the species chosen. Thus, for inhalation toxicology the rat has traditionally and justifiably been used as the model for man. There are, however, some human responses which the rat is unable to mimic, and vice-versa. When, for instance, it is suspected from structure-activity relationships or other information that a chemical may have sensitising potential, the rat is unsuitable. The guinea pig is a better, but still imperfect, model for human hypersensitivity especially since the lung is a target organ for an allergic reaction to exposure by inhalation. The guinea pig is also a better model than the rat for measuring lung mechanical changes (Amdur and Mead, 1958).

The susceptibility of the animal in relation to that of man should also be considered. This is especially important for delayed or

chronic effects from prolonged or repeated exposures at low levels, since little is known about the variation in susceptibility between species. The ratios of susceptibility in different species at lethal or near-lethal levels are often quite different from the ratios of delayed or chronic effects arising from prolonged, low-level exposure. Thus the one ratio should not be deduced from the other.

2.2. Dose

2.2.1. Intake and effective dose. With respect to systemic effects, the determining factor for the biological response to a chemical (whatever the route or routes of exposure) is the concentration in the target tissue, which depends on the amount absorbed into the body. The ultimate toxicant may not be the compound to which the subject is exposed. The exposure level merely describes the concentrations available to the subject. Thus in extrapolating data from experimental animals to man it would be more relevant to use the no-effect dose instead of no-effect concentration because the dose taken in by man differs, relatively, from that taken in by an experimental animal exposed to the same concentration, for the following reasons :

i) whereas man breathes through the nose and mouth, the rat breathes only through the nose. This is of especial relevance for particulates and irritating, soluble gases.

ii) the minute-volume of inspired air per kg.body weight (kgbw) in the rat is up to 10 times that for man. This means that, provided that the absorption pattern is similar in both species, man will absorb up to 10 times less of an inhaled vapour or gas than will rodents under identical conditions of exposure. It has been proposed that the extrapolation from experimental animals to man be based on comparative body surface-area rather than body weight, but this practice has not been generally adopted.

iii) the amount of inhaled material retained in the body will depend, in part, on the proportion exhaled, and this may vary between species.

iv) as well as exposure by inhalation, the experimental animal often has an additional oral, and at times dermal, exposure because of contamination of the available food and drinking water, and because it licks its contaminated fur. The human worker may have additional exposure from community air, food and water, and from dermal exposure at the workplace, etc.

All these factors must be taken into account in determining the total daily intake of the experimental animal and man. In most cases there are insufficient data to permit extrapolation of the effective dose in experimental animals to man. Occasionally the dosimetric formula of Weston and Karel (1946) may be helpful.

Thus, because the above factors have to be taken into account, the extrapolation can be carried out only on a case by case basis.

When the systemic effects of defined exposures in different species are being compared, the exposures should be expressed as the uptake in mg/kgbw per unit time. For inhalation this is determined by the minute-volume per kgbw during the study period. Most toxicological studies have been carried out with rats, and for this animal the quoted literature values of minute-volume vary widely. This variation is due to many factors, among which are : methodology (particularly the use of anaesthetics), age, strain, and the condition and conditioning of the animal. Palacek (1973) showed that rats weighing 230 g. had a mean minute-volume of 203 $\pm$ 14.5 ml., in agreement with results published by Kleinman and Radford (1964) and Stahl (1967). An average minute-volume per kgbw for the rat is therefore about 0.9 l. The corresponding figure for a 70 kg man at rest is 0.09 l. per kgbw. At a defined atmospheric concentration of a gas or vapour, the intake per kgbw in unit time for a rat would therefore be up

to 10 times higher than for man. This has to be taken into account when determining the safety factor.

2.2.2. Dose-effect relationships. The relation between a specific effect and the doses resulting from exposure at various concentrations may be expressed as a dose-effect relationship. To be useful for subsequent evaluation, animal experiments should clearly demonstrate such relationships since the slope of the dose-effect curve is essential for assessing the margin of safety, and it is necessary to be able to differentiate between background responses and exposure-related effects.

In interpreting dose-effect curves there are some important points to be taken into account. Usually there is a linear relationship between dose and effect only for that part of the curve between about 25% and 75% of the maximal effect. In any animal study, therefore, it is important to establish not merely a part of the dose-effect relationship but where that part lies in relation to the whole curve. For any specific effect of a substance there is a dose which produces a maximum response. Increasing the dose beyond this produces no further increase in effect. The importance of an increase in dose is reflected by the slope of the dose-effect curve. For instance, a curve with a steep gradient implies that changes in dose will produce relatively large changes in effect. In terms of toxic effects, a change of dose would be more critical in this case than it would for a substance with a shallower gradient.

2.3. Special considerations regarding inhalational and oral intake

2.3.1. Inhalation of particulates and fibres. In considering the relevance to man of animal studies on the inhalation of particulates (dusts or aerosols) and fibres, the amount of the particulate or fibre deposited in the airways, and the site of deposition are important. Although the way in which the physical properties of particles govern the rate and extent of deposition in the human airways has received

considerable attention (Walton, 1977), rather less is known about this for experimental animals. Thus the extrapolation of animal data to man is so complex, and is governed by so many factors, that it requires special expertise and judgement on a case by case basis.

The extent to which a substance can penetrate into the lower respiratory tract depends upon · i) for aerosols, the size and rate of evaporation of the droplets, and ii) for dusts, the particle size. It should not be forgotten that liquid or solid particles of a size above about 10 microns may be deposited before they penetrate the lower respiratory tract, and may be absorbed through the mucous membrane or by subsequent swallowing. Thus, apparently equal concentrations of a chemical dust or aerosol may have quite different physiological and toxicological effects because of differences in particle size and/or particle size distribution.

The factors described above and the existence of differences in the anatomy and physiology of the respiratory tract between species, preclude the extrapolation of animal data to man according to a simple mathematical model.

2.3.2. Extrapolation of data from one route of exposure to another

Ideally, in experiments on animals the route of exposure to the chemical should be the same as that expected at the workplace. However, inhalation data are often lacking and it is then necessary to use information from oral, or other, routes of exposure for deriving health-based limits. Such data must be used with great care because there is no constant conversion factor for extrapolating from one route to another. Different routes of entry of the compound into the body may lead to quantitative differences in the distribution of the compound after oral, dermal or inhalational exposure. This may lead to quantitatively and/or qualitatively different responses.

Extrapolation from the ratio of the single, acute oral and respiratory toxicities (LD50/LC50) to the ratio of the sub-chronic oral and respiratory no-effect levels, is invalid.For measuring the oral LD_{50}, a single oral dose is administered by gavage and this is, by definition, a "massive" single dose administered in half a minute and overwhelming the defense/metabolic mechanisms of the animal. The respiratory "dose" for calculating the respiratory LC_{50} (concentration in air) is absorbed over a time-span of 4-6 hours and is therefore much more amenable to metabolism and orderly elimination than when the chemical is administered orally. In addition, the longer term, low-dose effects from a chemical toxicant are in many cases quite different from the acute, high-dose effects.

It is often stated that substances absorbed via respiratory and intravenous routes do not pass the liver. This is not correct. They do to some extent, not during the first pass but subsequent to this, via the portal system and the hepatic artery on re-circulation. Some liver function tests are based on this principle. However, parenteral absorption is quicker and this is important in considering LD_{50}s and LC_{50}s, but in subchronic and chronic conditions the difference in rate of absorption may be much smaller. On the other hand, differences in metabolism due to a first-pass effect in the liver may be of special importance.

2.4. The extrapolation of metabolic, toxicokinetic and toxicodynamic data

Certain principles regarding the extrapolation of metabolic, toxicokinetic and toxicodynamic data need to be taken into account in interpreting animal data. Metabolism and toxicokinetics are concerned with the fate and effects of a chemical which depend upon its absorption and transport, distribution, and metabolism and elimination. The distribution of the compound in the organism by diffusion, passive transport or through a carrier in an active transport system, influences both the metabolism of the compound and the reactions at the receptor sites. These in turn may vary according to the species, sex, age, health status, etc.

Toxicodynamics is concerned with the biological response. This may be characterised by reversible or irreversible effects which are not always clearly distinguishable, so that very careful interpretation is necessary when considering the extrapolation.

Interspecies differences in biological functions are important since they lead to variations in the fate and mode of action of a chemical in an organism. Physiological differences in respiratory morphology and functions have also to be considered as they may lead to quantitatively and qualitatively different reactions in e.g. rodents and man.

For materials which are metabolised it has been suggested that the extrapolation of animal doses to equivalent doses in man should be based on the rule that the capacity for metabolism and elimination is proportional to basal metabolism. This, however, is not always so because the capacity for activation, inactivation and elimination depends on the activity of specific enzymes, which may vary quantitatively between species, and which is not necessarily proportional to general basal metabolism. Although general basal metabolism, i.e. oxygen consumption, is as a rule proportional to body surface, the activity of specific enzymes may not be so related, and this relationship is often unknown for inhibitors of specific enzymes (e.g. cyanides, certain organophosphorus compounds and heavy metals).

Neither the accumulation of a substance in the body nor the cumulation of repeated effects are necessarily related to the seriousness of the effect (for example, delayed neuropathy and vinyl chloride disease). Therefore the speed of elimination of a substance from the body is not necessarily related to the degree and ultimate result of the intoxication. In many cases the proportionate number of target cells would be more relevant than body surface in comparative pathology, so that comparison on a body weight basis would apply.

Finally, for a particular chemical, fundamentally different reactions may occur depending on whether exposure is continuous or intermittent. Depending on absorption and metabolism an effective

dose may be totally eliminated between daily exposures at the workplace. Alternatively, a residue of the dose may not be eliminated, or recovery from an adverse effect may not occur, before the next exposure, and this may lead to an accumulation of the substance and/or effects.

2.5. Depth of information available.

The toxicity of a chemical is normally assessed in a sequence of animal studies, and the confidence in a health-based limit derived from such studies naturally increases with their depth.

A limit derived only from the results of acute tests would have little value, although where it relates to a specific effect, eg. respiratory irritancy, it could be derived from a study of this effect only. Data from a sub-acute (2 to 4 week) study is the minimum basis from which a health-based limit may be derived. Sub-chronic (90-day) and chronic studies may reveal more subtle responses and the extra information from them will influence the size of the safety factor chosen, and increase the reliability of the exposure limit subsequently derived. It is noted that there are some effects, such as atrophy, hypertrophy, hyperplasia and metaplasia which are not always revealed by a 90-day study.

3. Other Factors.

3.1. Differences between occupational exposure and experimental conditions.

While animal experiments are designed to imitate as closely as possible the conditions of human exposure, not all aspects of these conditions can be realised experimentally. The idealised and controlled exposure conditions in animal experiments differ significantly from workplace situations.

In oral experiments, animals are usually exposed continuously for 24 h/d, 7 d/w, and in inhalation studies exposure is normally 6 h/d, 5d/w. Deviation from the planned exposure concentration is minimal in both cases. Studies involving oral exposure via food are

considered the most rigorous since stress is put onto the biological system without interruption, sometimes for the whole life of the animal. Studies in which a single large dose is administered to an animal by gavage need particularly careful interpretation (see also section 2.3.3). By contrast, human exposure at the workplace is by no means constant and is always discontinuous, depending on the actual work situation, eg. shift periods, interruptions during the shift and the conditions under which the compound is handled in practice.

Thus, in deriving health-based limits and choosing safety factors, the following points must be taken into account :

i) In occupational practice one has to protect adult workers, 16-65 years of age, in a reasonable state of health, more or less selected and generally under medical supervision by an occupational physician. Individuals who are very susceptible to specific substances are usually not occupationally exposed.

ii) The actual exposure is usually less than 8 hours per day, mostly 5 days per week, and certainly less than 52 weeks per year.

iii) The concentration in the air at the workplace is rarely constant, but fluctuates.

iv) Whereas laboratory animals are usually exposed to a single substance under controlled conditions, man is usually exposed to a variety of materials.

Even at one and the same workplace, exposure will differ from worker to worker, as demonstrated during surveillance studies based on personal sampling techniques. It will also depend on individual physique and habits, personal hygiene and training. The individuality of human beings is not reflected in the very uniform, often inbred, populations of laboratory animals. Finally, for the same concentration of a chemical in the air, the total uptake by a human being at the workplace will normally be less than the equivalent uptake of experimental animals because normal working

practices which minimise uptake are totally lacking in animal studies.

Thus, under comparable conditions of exposure the intake of a contaminant by humans will be less than that of the experimental animals, and in certain cases there may be no need for any safety factor in extrapolating animal results to humans.

3.2. Long-term exposure to local irritants.

In the ambient air of the workplace there are quite often low concentrations of chemicals with a local irritant effect in the lower respiratory tract, which may ultimately result in functional and structural bronchoconstriction, emphysema, fibrosis, and (particularly in rodents) pulmonary lymphadenopathy. Extrapolation across species, as well as from higher to lower concentrations, is extremely difficult in these cases, and this, together with differences in anatomy and breathing physiology (see section D.2.2.1), makes the use of simple mathematical models invalid.

3.3. Combinations of risk.

In contrast to the well-controlled exposure of the disease-free laboratory animal to a single substance, man is exposed to a variety of materials and is not necessarily free of disease (see also section D.1.3. on epidemiology).

At the workplace man is usually exposed to more than one chemical. In addition he may be exposed to substances arising from non-occupational activities such as tobacco, alcohol, lead in drinking water, etc. In particular, tobacco smoking has a wide spectrum of effects on the airways, including reduced clearance of inhaled particulates because of ciliary toxicity, enhancement of the penetration of material into the smaller airways, cardiovascular effects resulting from the sometimes very high circulating levels of carboxyhaemoglobin, etc. Such considerations emphasise the limitations of the animal model and may have to be taken into account in choosing a safety factor. They constitute an additional

reason why the use of simple mathematical models is not valid and a case by case approach is necessary.

3.4. Derivation of a no-adverse-effect level (NAEL) from a minimum-adverse-effect level (MAEL).

Where an NAEL has not been established but it has been shown that a certain exposure corresponds to a minimum adverse effect level (MAEL), it has been suggested that an NAEL be derived on the basis that "Usually, the MAEL will not be larger than 2-4 times the NAEL" (Zielhuis and van der Kreek, 1979a). No supporting evidence was provided for this important statement. Obviously this factor depends on the slope of the dose-effect curve, on the distance between successive dose levels chosen by the investigator, and on the kind of effect observed at the MAEL. In view of this it is clear that deriving an estimated NAEL from an observed MAEL is a matter of expert scientific judgement and cannot be done by a simple, generalised calculation.

For a species whose metabolism is not dissimilar to that of man and which exhibits a special susceptibility to a substance, it can be assumed that the human population is at least as susceptible (Zapp, 1977) and that extrapolation of the animal no-adverse-effect level to man is valid. But it is not possible to extrapolate a concentration which produces an effect in an animal to derive a no-adverse-effect level in humans. Hence, again, the prime importance of establishing the no-adverse-effect level in animal experiments.

E. CONCLUSIONS

For many substances which have been in use for quite some time the available toxicological data are limited. This situation, however, is not improved by the use of mathematical models. The best mathematics does not make poor data good, and does not compensate for the lack of information. However, when available, data on humans and animals have to be, and can be, used for deriving health-based limits for the occupational exposure of humans to

airborne substances. In the choice of safety factors to be applied to such data for this purpose, the use of generalised mathematical schemes is to be deprecated because of the many factors which must be taken into account. It is difficult to appreciate how a general mathematical model could accomodate both the wide variations in animal and human response and the variable quality and quantity of much of the data available.

There is no alternative to the use of expert scientific judgement in this matter.

F. BIBLIOGRAPHY

- Amdur, N.O. and Mead, J. (1958). Mechanics of respiration in un-anaesthetised guinea pigs. Am. J. Physiol., 192, 364-368.

- ECETOC (1982). Risk Assessment of Occupational Carcinogens, Monograph No.3.

- Kleinman, L.I. and Radford, E.P.(1964). Ventilation standards for small animals. J. Appl. Physiol., 19, 360-362.

- Palacek, S.F.(1973). Measurement of ventilatory mechanics in small laboratory animals. Acta. Univ. Palacki Oloumo. Fac. Med., 65, 311-312.

- Stahl, W.R. (1967). Scaling of respiratory variables in animals. J. Appl. Physiol., 22 (3), 453-460.

- Walton, W.H., ed.(1977). Inhaled Particles IV, Pergamon Press, Oxford, UK.

- Weston, R.E. and Karel, L.(1946). An application of the dosimetric method for biologically assaying inhaled materials. J. Pharmacol. Exp. Ther., 88, 195-207.

- WHO (1981). Recommended Health Based Limits in Occupational Exposure to Selected Organic Solvents. Technical Report Series n° 664, P. Geneva.

- Zapp, J.A.(1977). Extrapolation of animal studies to the human situation. J. Tox. Environ. Health, 2, 1425-1433.

- Zielhuis, R.L. and van der Kreek, F.W.(1979-a). Use of a safety factor in setting health based permissible levels for occupational exposure. Int. Arch. Occup. Environ. Health, 42, 191-201.

- Zielhuis, R.L. and van der Kreek, F.W.(1979-b). Calculation of a safety factor in setting health based permissible levels for occupational exposure. Int. Arch. Occup. Environ. Health, 42, 203-215.

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