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CURRENT PRINCIPLES OF HYGIENIC STANDARDS SETTING (Part II)

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Abstract. The paper presents general principles of setting the hygienic standards for substances of threshold effect and nonthreshold agents.

The authors introduced the mathematical models used for quantitative risk assessment and models for assessment of the dose-response relationship according to the pyhsiological principles.

GENERAL PRINCIPLES OF DERIVATION OF THE RECOMMENDED EXPOSURE LIMITS FOR THE SUBSTANCES OF THRESHOLD EFFECT

Epidemiological studies, medical records and experiments on animals constitute a basis for the OEL determination The highest doses or chemical substance concentrations which, based on the results of experiments or observation, may be considered as those not inducing any adverse effects in the form of morphological changes, functional or developmental disorders and not conducive to shortening of the expected life-span, are usually the starting point. Such concentrations are determined shortly as non observed adverse efect level (NOAEL) and they are usually expressed in mg/kg of body weight/day.

Frequently there are some difficulties in determining NOAEL based on the results of epidemiological and experimental studies carried out on humans, except for the chemical substances which after a short-term exposure produce reaction in the form of a local irritation. Therefore, NOAEL values are mostly derived from the results of experiments on animals.

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When the principal toxicological data do not allow to determine NOAEL, an attempt should be made to determine the lowest dose or substance concentration which produce in a group of humans exposed or animals subjected to exposure a noticeable adverse effect, in the same form as in the case of NOAEL. Such doses or concentrations are determined as the lowest observed adverse effect level (LOAEL).

The definitions quoted here, adopted in various countries and by various agencies, may vary, e.g. the definition proposed for NOAEL in USA is: "An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between exposed population and its appropriate control; some effects may be produced at this level, but they are not considered as adverse, nor precursor to specific adverse effect."

Actually, the meaning of those two definitions is the same, they differ only in the degree of the minuteness and precision. Frequently enough, especially in the case of Env. EL determination, the highest exposure levels, (i.e. the highest doses or concentrations observed in the exposed people), at which no biologically distinguishable changes, as compared with those observed in the corresponding control group, are detected, are assumed to be the starting point. These are referred to as non observed effect level (NOEL). In many discussions opinions are presented that NOAEL is in fact brought to NOEL, although in many instances NOEL is much lower than NOAEL.

Further simplified procedure used sometimes for deriving OEL involves dividing the NOEL exposure by an arbitrarily selected safety factor. Very illustrative is the example quoted by Leung and Paustenbach (15) relating to the method of determination of TLV for phenyl ether: "Data: a repeated inhalation study of exposed rats, rabbits and dogs at mean concentrations of 5 and 10 ppm phenyl ether vapor for 7h/day, 5 days/week for a total of 20 exposures. No signs of toxicity or irritation were observed in animals exposed to 5 ppm.

$$\text{TLV} = \frac{\text{NOEL}}{\text{safety factor}} = \frac{5 \text{ ppm}}{5} = 1 \text{ ppm}$$

The recommended TLV for phenyl ether is 1 ppm as a time-weighted average".

Such simplified procedure refers in particular to chemicals, which exert chiefly the irritative effect.

Considering the historical development of Env. EL it should be admitted that the concept of ADI (acceptable daily intake) adopted in the early sixties (Joint FAO/WHO Expert Committeee on Food Additives, 1961) played an important role both in the determination of Env.EL, and in the activity known as Risk Management. ADI was obtained by dividing NOEL by the safety factor (presently referred to as uncertainty factor), which accounted for the possible differences in the sensitivity between test animals and people. Originally, ADI determined the quantity of a chemical which could be swallowed by people everyday during their lifetime without causing adverse effects.

A several year long discussion on the assumptions and concepts for the determination of EL, on the procedure to be adopted depending on the volume of available information and its reliability, has modified procedures employed and made it possible to develop a number of new indicators enabling quantitative evaluation of the relationship between exposure level and its consequences. The probability of accurate determination of EL values has been thereby increased.

During the recent 2–3 years, it has been suggested to replace the conventional ADI derived from dividing NOAEL by the safety factor of 10 or 100, by a new indicator, the reference dose (RfD), which determines the exposure levels or absorbed doses tolerated by people. This concept has been developed at US EPA and presented in a paper by Barnes (3). The concept has resulted from the critical evaluation of ADI, especially as used for the purpose of regulatory decision making. The criticism related, among others, to:

– the terms "acceptable" and "safety factor", suggest absolute safety of ADI; where in fact ADI is, by no means, a measure of safety;

– ADI does not have any degree of significance which may be scientifically justified;

– there is a real chance of obtaining different ADI values from different test programs, and there are possibilities for selecting different critical effects, which make it difficult to decide on risk management and may cause confusion.

The reference dose can be expressed by the formula:

$$RfD = \frac{NOAEL}{(UF \times MF)}$$

where UF is the total uncertainty factor, and MF is a modifying factor.

The following recommendations were set forth in the work by Barnes (3), based on the publications by Durson and Stara (11) for the application of the uncertainty and modifying factors during introducing the reference doses:

Use a 10-fold factor when extrapolating from valid experimental results in studies using prolonged exposure to average healthy humans. This factor is intended to account for the variations in sensitivity among the members of the human population and is referenced as 10 H;

– Use and additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans and is referenced as 10 A;

– Use an additional 10-fold factor when extrapolating from less then chronic results on experimental animals when there are no useful long-term data. This factor is intended to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs and is referenced as 10 S;

– Use additional 10-fold factor when deriving a RfD from LOAEL, instead of NOAEL. This factor is intended to account for the uncertainty involved in extrapolating from LOAELs to NOAELs and is referenced as 10 L;

– Use professional judgment to determine the MF, which is an additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertaity of the study not explicitly treated above, e.g. the completeness of the overall data base and the number of species tested. The default value for the MF is 1".

The work by Barnes, in the final stage of risk evaluation referred to as "risk characterization", which served as the starting point for risk management, contained the following recommendations:

a) synthesize and summarize all data accounted for in the conclusion on the character and scope of the risk:

b) justify the qualitative conclussion on the probability that the chemical can pose hazard to humans;

c) discuss the information on dose-response relationship taken into account during RfD derivation, together with the UF and MF used;

d) analyze data which determine shapes and slopes of the curves for different types of toxic effects and for the corresponding doses (exposures) for the various endpoints, data relating to toxicokinetics (absorption and metabolism), and the nature and severity of the effects observed;

e) prepare estimates of the nature and scope of the exposure and of the types of people exposed;

f) discuss general uncertainty in the analysis, taking into account assumptions made, scientific judgments employed and the degree of conservatism used.

From quite a superficial analysis of the recommendations on the magnitude of the safety factors it can be seen that, except for MF, which is associated with the completeness of the information underlying RfD, all other factors have a constant value of 10; if the recommendations were used automatically, total UF value could be as high as 10^5. For quantitative experiments on animals, total UF is 100 and it is quite probable that an additional low-value MF factor shall be introduced.

Thus, NOAEL-to-RfD conversion involves basically accounting for the differences between the species and the differences between individual people.

However, a number of questions remain to be answered:

1. how great the UF + MF factor can be without evoking doubts as to the basis from which the RfD value and its EL derivative have been derived?

2. what is the effect of the differences in sensitivity within the tested animal species on the total UF?

3. what is one supposed to do when the tested animal species exhibits higher sensitivity than persons of an average health status?

4. to what extent does a procedure, assumed to be correct for the derivation of Env. EL relating to the uncertainty factors, correspond to procedure of OEL determination.

The proportion of the differences in toxicodynamics and toxicokinetics between humans and animals also requires an explanation. All those remarks show that studies on the application of the uncertainty factors should be continued.

In situations where the results of tests on people and/or animals are not suitable for determination of NOEL and NOAEL while enabling, however, determination of LOAEL, it is recommended to analyze dose-response relationship and to try to determine the benchmark dose. The benchmark dose is determined on the basis of all results obtained in a specified toxicologic investigation having the investigated effect for its object. For obvious reasons it is desirable that a specified benchmark dose should correspond to low frequency of effect occurrence (e.g. 0.1% or less).

Some explanation on the use of the UF factor in the case when one of the tested animal species, i.e. rat, has proved to be more sensitive than humans is contained in the "Criteria for a recommended standard" published by NIOSH in 1990, referring to occupational exposure to ethylene glycol monobutyl ether and ethylene glycol monobutyl ether acetate. The document is also a good example of conversion of the retained dose for rats exposed (at NOAEL) to an equivalent exposure concentration for humans, as well as of direct OEL derivation from NOAEL with only one UF = 10 (6).

Taking into consideration the differences between OELs and Env.ELs, the latter are considered from the point of view of total exposure to a specified substance resulting from all environmental media in which it is present i.e. ambient air, food, drinking water and possibly soil. This requires a procedure which would enable to determine the proportion of tolerable doses of substances absorbed by the human organism through different routes from various environmental media.

Mathematical models are sometimes used for threshold factors to determine the relationship between the dose and the risk of adverse health effects in persons exposed. In such case the doses of toxic substances absorbed into the organism are usually within such quantitative values range, all of which are over the threshold value. These models are almost the same as the non-threshold ones (e.g. multistage, one-hit, Weibull) and they rise the similar doubts chiefly because the relationships found owing to them cannot be confirmed or validated by others.

SETTING THE HYGIENIC STANDARDS FOR NON-THRESHOLD AGENTS – OF THE CURRENT SITUATION

For quite a long time, scientists and groups of experts providing the bases for the actions aimed at reducing the adverse health effects induced by the carcinogens present in the occupational environment as well as in the communal environment media, have not presented any draff proposals for the recommended exposure limit.

This has been due to adopting the conception on the "non-threshold" effect of carcinogens and the resultant inability to determine safe exposure levels. Setting the legally binding standards usually is a responsibility of the governmental administration or scientific institutions charged with this task by the administration, authorized to decision making and responsible for the legislation in this respect. The tendency to avoid making any suggestions of the kind is alo a consequence of the obligation to take into account all sorts of circumstances, feasibility of standards observation and cost-benefit analysis. Hence, delay in taking relevant decisions or setting standards at levels other than those recommended has been and continues to be a common practice.

For "non-threshold" agents, such as carcinogens, currently prepared health criteria, instead of suggesting EL, comprise assessment of the risk caused by a determined exposure level or the doses absorbed into the human organism. Since the early '70s, more and more attention has been paid to the risk evaluation, first among researchers, next in the society and finally in the legal regulations. This concern has resulted from the fact that the risk assessment methodology allowed not only to determine quantitatively the possible adverse health effects exerted by environment contamination and classify the carcinogenic agents according to their potential but also to anticipate the probability of manifestation of these effects induced by the exposure to much lower levels than those presently found. This facilitated to predict the effectiveness of preventive actions aimed at reducing the exposure. Hence, the risk assessment comprised in the currently prepared health criteria furnish the authorities responsible for health policy, with the complete information. Provided with the information they are able to make appropriate decisions, according to the current state of our knowledge and methodology.

High qualicifations and experience of experts who develop the health criteria are a prerequisite for accurate decisions to be made in future. There are, however numerous and serious objections particularly with regard to extrapolation from high doses and concentrations to very low ones due to discrepancies in the assessment made by researchers or groups of experts using various models of risk estimate. As these discrepancies may even reach three orders of magnitude, some authors are of opinion that the use of mathematical models for assessment of the dose-response relationship at very low dose levels, in spite of the differences and a lack of possibility of biological verification is provoked by the pressure of the control agencies which require that relatively safe exposure levels be determined.

QUANTITATIVE RISK ASSESSMENT AS A BASIS FOR SETTING THE HYGIENIC STANDARDS FOR NON-THRESHOLD AGENTS

Evaluation of the risk, due to human exposure to carcinogens, using the animal studied as the starting point is based on the following assumptions:

– the relationship between the dose administered (measured with the appropriate units) and frequency of occurrence of tumor in animals is determined on the basis of animal bioassay,

– the dose-response relationship in humans is the same as that in animals,

– the appropriate units for the equivalent dose may be both mg/kg of body weight per day and mg/m^2 of body surface per day,

– the carcinogenic response after administration of low doses is linear.

In the absence of toxicokinetic data the risk assessment is exclusively a function of the dose introduced into the organism. It is essential to determine the equivalent doses for man and aninmals subjected to experiments. The equivalent dose may be expressed in two ways; either in the form of quantity per unit of animal body weight i.e. mg/kg of body weight or a quantity per body surface i.e. mg/m^2 of body surface. Taking into account that it is hard to measure empirically the animal body surface, it has been adopted that body weight raised to the power of 2/3 marked with symbol $(bw)^{2/3}$ is the body surface measure.

The supposition, that $(bw)^{2/3}$ is a relevant measure for the dose equivalent determination is supported by the study of Freireich et al. (13). It is based on the assumption that metabolic rate is proportional to body surface and not to body weight.

The studies on the dose-response relationship are usually carried out at least in two animal species. The principle has been adopted that, for evaluation of the risk of cancer in humans, the most sensitive animal species should be taken into account as well as the most statistically sensitive tumor form and site.

Sometimes, the risk analysis is based on both the data obtained in epidemiological studies carried out among the groups of persons exposed and on the data from experiments on animals.

The risk assessment usually involves calculation of individual risk increase, the number of excess cases and evaluation of the impact of various sources of error on the results obtained. For chemical agents, viewed to have zero threshold, due to the fact that the doses of the tested substance administered to animals are most frequently much higher than the doses absorbed by the persons exposed, it is

indispensable to use the relevant mathematical model which, on the basis of the experimental data, allows to determine the probable dose-response realtionship for the low dose region.

BRIEF CHARACTERISTICS OF THE MATHEMATICAL MODELS USED FOR QUANTITATIVE RISK ASSESSMENT

In principle, any mathematical model may be used to fit the experimental data determining the dose-response relationship on condition that it permits to predict responses to the doses outside the experimental range. In the case of chemicals of non-threshold action, the real shape of the curve showing the dose-response relationship in the subexperimental range of doses, is unknown.

Nevertheless, there is a need for hypothetic determination of the relationship if we wish to determine as precisely as possible, the environmental risk which could be accepted whenever it is not feasible to avoid it. Some time ago, three – categories of mathematical models of extrapolation were suggested to illustrtate the relationship between the dose rate and response in the subexperimental doses range:

– tolerance distribution models (probit, logit and Weibull),

– mechanistic model (one-hit, multi-hit, multistage and linearized multistage models),

– time – to – occurrence models (lognormal, Weibull, Armitage-Doll and Hartley-Sielken's models),

There may also be used individual mathematical models: linear, quadratic and linear-quadratic.

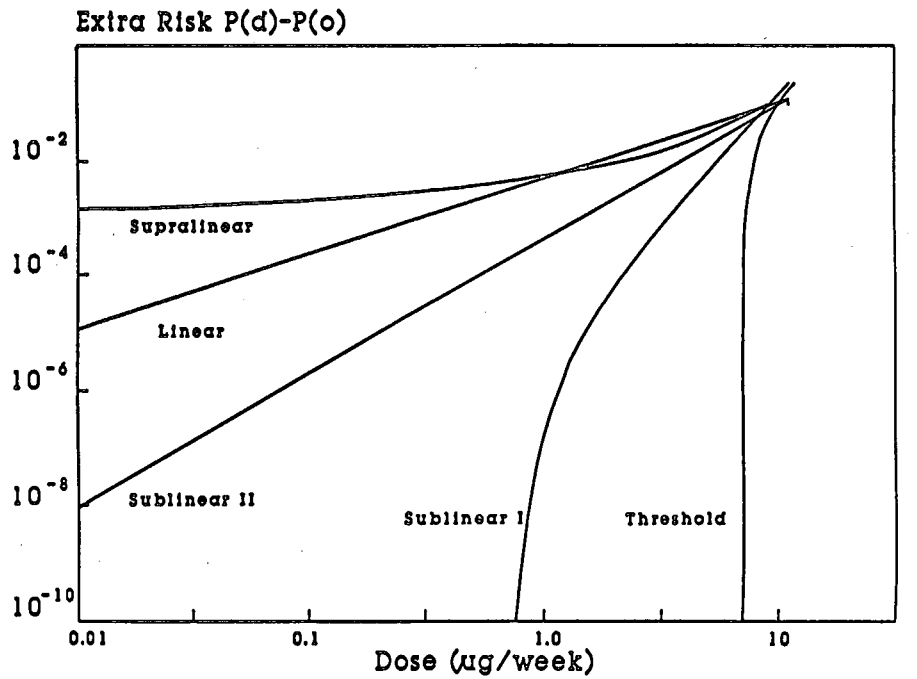

Fig. 1. A comparison of the results of various dose-response models for the high and low-dose regions. From NAS (1983).

Each of these models allows, to a similar extent, to adjust the experimental data, therefore, it is difficult to recommend the selection of one of them. It is known, however, that the results of extrapolation may differ significantly depending on the model used. It is illustrated by Fig. 1.

It seems purposeful to quote characteristices of models of extrapolation from high to low doses comprised in the work of Munro and Krewski (19).

"Stochastic models are based on the premise that a positive response is the result of the random occurrence of one or more biological events. The one-hit model is based on the concept that a response will occur after the target site has been hit by a single biologically effective unit of dose. The multi-hit model is a direct extension of one-hit model, assuming that more than one hit is required in order to induce a response. (This model may also be viewed as a tolerance distribution model, where the tolerance distribution is gamma. This formulation allows the "hit" parameter k to assume non-integral values). The multi-stage model, on the other hand, is based on the assumption that the induction of irreversible self-replicating toxic effects such as carcinogenesis is the result of the occurrence of a number of different random biological events, the time rate of occurrence of each event being in strict linear proportion to the dose rate (7, 8). Despite their biological rationale, these stochastic models must also be considered somewhat arbitrary until the mechanisms of carcinogenesis are more fully understood.

The shape of the dose-response curves for the above models in the low-dose region will have considerable impact on estimates of risk associated with low levels of exposure. For example, the one-hit model is linear at low doses and will thus generally provide relatively high estimates of risk at low dose levels. The logit, Weibull an multi-hit models are linear at low doses only when the shape parameters ß, m and k in these models are equal to unity. When these parameters are greater than unity, the dose-response curves for these models approach zero at a slower than linear, or sublinear rate. The multi-stage model is linear at low doses only when the linear coefficient in the model (β_1) is positive and is sublinear otherwise. The probit model is inherently sublinear at low doses and generally leads to relatively low estimates of risk at low doses levels. (Mathematically, the probit model is extremely flat in the low-dose region, with the dose-response curve approaching zero more rapidly than any power of dose)".

Low-dose risk extrapolation may be carried out by means of various procedures. The most popular is linearity model procedure. It is best illustrated by the figure comprised in the work of D.J. Paustenbach (Fig. 2) (20).

The popularity of linear models may be attributed to the fact that they allow to anticipate the risk higher than that actually occurring. Therefore, they ensure better safety margin, however, some of the recommendations based on the results obtained by means of these models cannot be applied in practice.

Assuming the linear model, the individual risk increase may be calculated according to the following formula:

$$P = R \times D_3 = R \times C \times I \times T_3$$

Where:

P = individual risk increase resulting from the determined dose
R = risk factor (in mg^{-1}) = excess risk per unit of dose derived from the lowest available experimental dose – response point

D_3 = individual dose in mg.
C = concentration in mg per unit of the contaminated environmental medium (e.g. air, drinking water, food)
I = intake in units of contaminated medium
T_3 = individual exposure time in days (adjusted if necessary for latency and the remaining lifetime from last exposure).

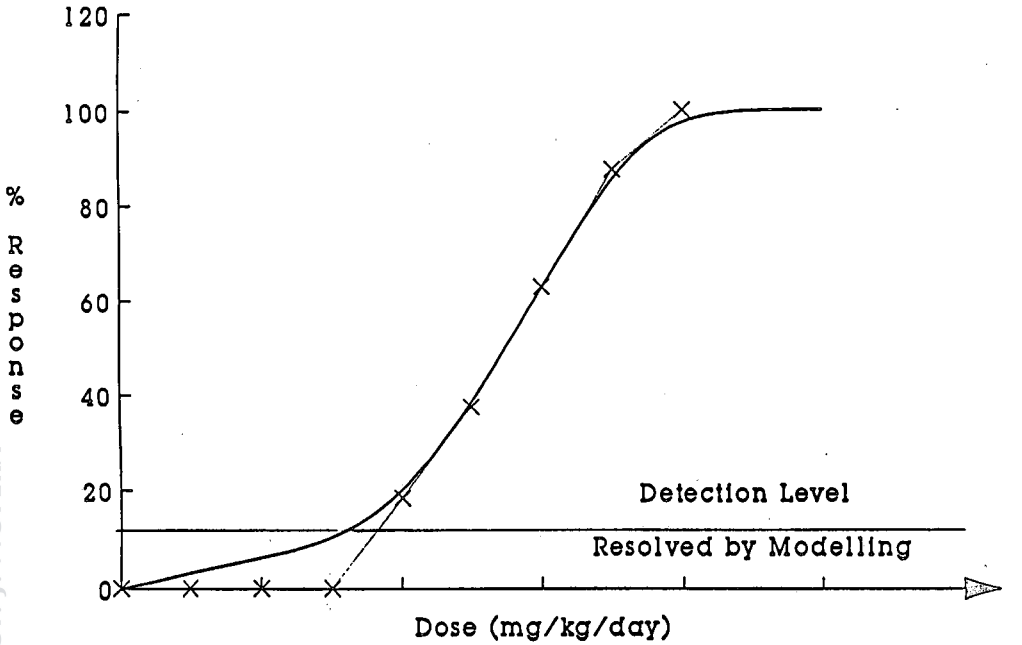

Fig. 2. Extrapolation of results obtained after experimental administration of low doses of carcinogen for the probable response to much lower dose. Experimental doses being located in five points of detection level.

According to this formula, the acceptable concentration may be calculated:

$$C = P/ (R \times I \times T_3)$$

The linearized multi-stage model is the most frequently used model for calculation of the dose-response curve with Crump's modifications published in 1980

$$P(d) = 1 - \exp [-(qo + q_1 d + q_2 d^2 + ... + q_k d^k)]$$

where: P (d) = lifetime risk (probability) of cancer at dose d the point estimate of the coefficients:

$$q\ i > 0,\ i = 0, 1, 2 ..... k$$

exp =, exponential function

Equivalently: incremental cancer risk, i.e. extra risk over background rate may be defined as:

$$A\ (d) = \frac{P(d) - P(o)}{1 - P(o)}$$

The point estimate and the 95% upper confidence limit of the extra risk (Ad) are calculated by means of the relevant computer programs (e.g. GLOBAL 83 and GLOBAL 86 used by US EPA). The 95% upper and the 95% lower confidence limit for the dose producing a given risk are determined from the 95% upper confidence limit: q^*_1 by q^*_1 parameter; when $q^*_1 = 0$ the extra risk at low doses tends to a form which may be expressed by the formula: $A(d) = q^*_1 \times d$. Therefore, it be may assumed that $q^*_1 \times d$ is the upper confidence limit for the extra risk R. R/q^*_1 is the approximate lower limit of confidence for the dose producing an additional risk (R). The upper limit of confidence calculated for additional risk from low-dose exposure is always linear. The slope q^*_1 is assumed to be the upper-bound chemical potency to induce cancer under conditions of low-dose exposure. It is worth mentioning that the application of a multistage model likewise other mathematical models requires the extrapolation of experimental data. This is done with the use of a special procedure. The details of applying the multistage model to fit it to low doses are discussed in the paper by E.L. Anderson et al. (2) and Health Assessment Document for Trichloroethylene, published by US EPA in July 1985 (14).

The risk of cancer is most frequently calculated for the whole lifetime. However, the basis for determining that risk in humans are the animal studies where the duration of exposure and the time of survival of test animals are usually shorter than the lifetime. Then the problem arises of calculating the risk of cancer for the whole period of the human lifetime. To explain the issue more thoroughly it sems advisable to refer to the US EPA document of 1985 (14), for trichloroethylene. According to this subchapter – "If the duration of experiment L_e is less than the natural lifespan of the test animal L, the slope q^*_1, or more generally the exponent g(d), is increased by multiplying a factor $(L/L_e)^3$. We assume that if the average dose d, is continued, the age-specific rate of cancer will continue to increase as a constant functions of the backround rate. The age-specific rates for humans increase at least by the 2nd power of the age and often by a considerably higher power, as demonstrated by Doll (11). Thus, we would expect the cumulative tumor rate to increase by at least the 3rd power of age. Using this fact, we assume that the slope q^*_1, or more generally the exponent g(d), would also increase by at least the 3rd power of age. As a result, if the slope q^*_1 [or g(d)] is calculated at age L_e, we would expect that if the experiment had been continued for the full lifespan L, at the given average exposure, the slope q^*_1 [or g(d)] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (5) and the time-to-tumor model considered by Daffer et al. (10) where the probability of cancer by age t and at dose d is given by

$$P(d, t) = 1 - \exp [-f(t) \times g(d)]".$$

MODELS FOR ASSESSMENT OF THE DOSE-RESPONSE RELATIONSHIP ACCORDING TO THE PHYSIOLOGICAL PRINCIPLES (BIOLOGICALLY MOTIVATED MODELS)

The considerable uncertainty pertaining to mathematical modelling has become the main reason for seeking solutions which could improve extrapolation from high to low doses as well as diminish possible errors associated with the applied risk assessment procedures. In 1984, Ramsey and Anderson published a report on

a procedure of extrapolation which allowed the use of pharmacokinetic data (21). The discussion on the model, called a physiologically-based pharmacokinetic model (PB – PK), has resulted in its extension, making it possible to incorporate all the biological data available as well as to consider viewpoints on cancer development (Clewell and Anderson, (4); Menzel (16)).

One has to admit that the development of the procedure described by Ramsey and Anderson (21) has been a considerable progress in risk assessment as they tried to find a way to apply biological data to mathematical modelling. The main advantage of the PB – PK model was the possibility of taking account of the administered dose of the toxic chemical and the dose absorbed by the target organ or tissue. The dose is referred to as the biologically relevant dose and the ratio between that dose and the dose at the onset of exposure depends on some pharmacokinetic mechanisms such as metabolim, distribution and elimination.

While assessing the biologically relevant dose one should consider many physiological data concerning both the test animals and the humans as well as the formulas reflecting the uptake, distribution, metabolism and elimination of the absorbed substance. Ramsey and Anderson published two Tables displaying the biological data and parameters used in their PB – PK model. The Tables are presented below.

The authors of the paper referred to admit that they had to make several assumptions and consider some values as tentative only while developing the model. The assumptions concerned among others the tissue classification and blood flow through different tissues. In the Appendix, Ramsey and Anderson included a series of

Table 1. Abbreviations and symbols used in describing a physiologically based pharmacokinetic model for inhaled styrene

BW	Body weight (kg)
Q_{alv}	Alveolar ventilation rate (liters air/hr)
C_{inh}	Concentration in inhaled air (mg/liter air)
C_{alv}	Concentration in alveolar air (mg/liter air)
C_{exh}	Concentration in exhaled air (mg/liter air)
N	Blood: air partition coefficient (liters air/liter blood)
Q_t	Cardiac output (liters blood/hr)
C_{art}	Concentration in arterial blood (mg/liter blood/
C_{ven}	Concentration in mixed venous blood (mg/liter blood)
V_{max}	Maximum enzymatic reaction rate (mg/hr)
K_m	Michaelis constant for enzymatic reaction (mg/liter blood)
	Subscript (i) for tissue groups or compartements:
	l Liver (metabolizing tissue group)
	f Fat tissue group
	m Muscle (lean) tissue group
	r Richly perfused tissue group
Q_i	Blood flow rate to tissue group (liters blood/hr)
V_i	Volume of tissue group (liters i)
C_i	Concentration in tissue group (mg/liter i)
A_i	Amount in tissue group (mg)
C_{vi}	Concentration in venous blood leaving tissue group (mg/liter blood)
P_i	Tissue: blood partition coefficient (liters blood/liter i)

Table 2. Physiological and biochemical parameters* used in describing the behavior of styrene in the pharmacokinetic model of Fig. 1

		Mouse	Rat	Human
Body weight (kg)	body wt	0.022	0.30	83.0
Alveolar ventilation (liters air/hr)	Q_{alv}	0.725	4.50	230
Blood flow rates (liters blood/hr)	Q_t	0.908	5.64	290
	Q_l	0.340	211	108
	Q_f	0.080	0.50	26.8
	Q_m	0.110	0.68	34.0
	Q_r	0.378	2.35	121
Tissue group volumes (liters)	V^1	0.00088	0.012	3.32
	V_f	0.00198	0.027	7.47
	V_m	0.0161	0.219	60.6
	V_r	0.011	0.015	4.15
Blood: air partition coefficient	N	40	40	52
Tissue: blood partition coefficients	P_l	2.7	2.7	2.7
	P_f	50	50	50
	P_m	1.0	1.0	1.0
	P_r	5.7	5.7	5.7
Maximum reaction rate (mg/hr)	V_{max}	0.58	3.6	184
Michaelis constant (mg/liter blood)	K_m	0.36	0.36	0.36

* The parameters for mice and humans were calculated from the parameters for rats as desribed in the text.

differential equations which quantify the time course of styrene concentrations within four tissue groups specified in Tables 1 and 2.

It is commoly believed that the application of the biologically motivated models of extrapolating the results of animal studies to humans will be most significant, especially when there are some data on human pharmacokinetics. However, the models of this kind require collecting many data which is both time-consuming and costly. Hence there is a tendency to limit the scope of the information and to base the toxicological and risk assessment on the results of short-term testing (cellular tests) and the physic-chemical data.

Another example of the use of pharmocokinetic data for the assessment of the risk of cancer from exposure to chemical carcinogens is the Health Assessment Document for Trichloroethylene included in the Final Report and Addendum to the Health Assessment Document for Trichloroethylene: Updated Carcinogenicity Assessment for Trichloroethylene, published by US EPA (1, 14). The data on the hepatolcellular carcinomas were elicited from a series of four sets of experiments in mice in which TCI was administered by oral gavage. They were the grounds for assessing the risk of cancer with the use of a linearized multistage model. The risk of cancer due to inhalation exposure was calculated using the extrapolation of data from oral studies.

The Addendum focuses on inhalation exposure in mice and rats. The results of a quantitative analysis of inhalation studies were similar to those discussed in the final report which were derived from oral studies. The upper-bound estimate of the incremental cancer risk from exposure to TCI at the air concentration of 1μg/m^3, for people exposed for a period of 70 years of their life as reported in the Final Report,

amounted to 1.3×10^{-6} while as in the Addendum to 1.7×10^{-6}. Both the Final Report (14) and the Addendum (1) are based on the same well-documented hypothesis that the carcinogenic potency of TCI is due to the presence of reactive intermediate metabolites in the reactive cells. The metabolites include e.g. TCI oxide, chloral, dichloroacethyl chloride, formyl chloride. They are believed to account for the hepatotoxicity of TCI, inducing morphological changes as well as dysfunctions and cellular genotoxicity. TCI oxide is assumed to be the most probable carcinogenic agent. An assumption was made that the amount of reactive intermediate metabolites is in proportion to the total amount of metabolized TCI. According to the Final Report data, one can collude that the metabolic pathways in man, mouse and rat must be similar. The results of the studies on TCI metabolism were used as a basis for determining the relationship between the dose given during an experiment (mg/animal) and the metabolized quantity. The Michaelis-Manten type of equation was applied, $M = a \times d\,(b + d)$, where d is the dose administered (mg/animal) and M the corresponding amount of metabolized TCI. The a and b parameters are determined by least-square estimates. Using the data included in the Final Report the lifetime average effective exposure (LAE) was calculated as follows:

$$LAE_M = \frac{104 \text{ weeks}}{104 \text{ weeks}} \times \frac{5 \text{ days}}{7 \text{ days}} \times \text{metabolized dose/mg/animal/day}$$

Then the human equivalent was determined: $LAE_M = LAE_H \times$ scaling factor. The 104 weeks in the formula stand for the period of a mouse lifetime whereas the symbols M and H refer to the mouse and human parameters, respectively. As the scaling factor the ratio of $W_H/W_A^{2/3}$ was used i.e. the principle of proportionality of the dose to the body surface in man and mouse. For instance the scaling factor for male mouse was $(70/040)^{2/3} = 145.21$.

On the basis of the study results concerning cancer incidence in rats as well as the calculated metabolized dose (mg/day), calculated human equivalents and lifetime average exposure, the slope coefficient (q*) for TCI was determined using a linearized multistage model. The geometric mean of q* for humans, taking into account the metabolized doses equivalence $(mg/kg/day)^{-1}$, amounted to 1.3×10^{-2}. The upper-bound estimate of the cancer risk from $1\mu g/m^3$ of TCI in the air was derived from the geometric mean of q* and the estimate of daily intake according to the data from human volunteer study reported by Monster et al. (18).

The discussion on some very few fragments of the documentation for trichloroethylene contained in the final report prepared by the US EPA cannot replace the complete methodology used to assess the magnitude of the risk or the methods of deriving the units of the risk due to the contamination of drinking water and atmospheric air with trichloroethylene. The discussion, however, shows that the PB-PK model was not utilized to the full extent. The authors of the supplement to the final report state that this was not possible due to the lack of various pharmacokinetic data.

The preparation of a quite similar procedure described by Ramsay and Anderson (21) was published by Travis et al. (22) in "Physiology-based pharmacokinetic approach for assessing cancer risk of Tetrachloroethylene". Without going into detalis of the particular chapters of this work and of the employed methodology, it should be noted that the incorporation of pharmacokinetics into the assessment of the risk resulting from exposure to tetrachloroethylene (perchloro-

ethylene) reduced risk assessment by a factor of approx 1.6. This is illustrated in one of the Tables (Table 3).

Table 3. Risk resulting from exposing people to 1 $\mu g/m^3$ tetrachloroethylene in air*

Method by body weight	Extrapolation by body surface	Extrapolation
Conventional method	5.1×10^{-7}	6.8×10^{-6}
PB-PK model	3.1×10^{-7}	4.3×10^{-6}

*According to C.C. Travis,R.K. White and A.D. Arms

APPLICATION OF THE ASSESSMENT OF RISK CREATED BY THE NON-THRESHOLD FACTORS IN THE PREVENTIVE ACTIVITY

It is generally recognized that the primary objective of quantitative risk assessment includes: characteristics of the expected types of changes in the health status; determination of the probability of those changes occurring in an individual; or the determination of the expected number of cases with the specified changes in health status among the exposed population. Another, also very important task of the carcinogenic factor risk assessment requires finding the answers to the question: to which group of carcinogens a given substance is to be classified or, using the US EPA terminology, what is the weight-of-evidence that the specified substance is carcinogenic to people (and not e.g. exclusively to the test animals). This information, together with the underlying data, constitute a starting point for the activity known as risk management. This activity includes various aspects, but relates primarily to setting priorities, to the determination of target levels and hygienic standards, as well as to balancing risk and benefits. Various governmental agencies, national or international organizations dealing with setting or suggesting allowable exposure limits use the concept of acceptable risk. The considered exposure duration differs, depending on whether the risk assessment relate to occupationally or communally exposed population. For occupational exposure, risk during working lifetime, i.e. during 45 years is generally determined. For the communal exposure, the appropriate risk relates to the whole lifetime, i.e. 70 to 75 years. For carcinogenic agents, acceptable occupational risk levels vary between 10^{-2} and 10^{-5}. Considering that workers may be exposed not only to one, but to a number of different carcinogenic agents, the acceptable working lifetime risk 10^{-5} seems to be more appropriate. The assumed acceptable lifetime risk levels resulting from the exposure of the general population to carcinogenic agents are usually 10^{-6}, but may very from 10^{-3} (e.g. for exposure to radiation) up to 10^{-8}, taking into account the size of the exposed population.

Although the upper bound risk estimates have many inherent uncertainties, they constitute at present the sole opportunity for the assessment of the relative risk values. The comparison of data including the nuimber of exposed people and the corresponding relative risk reflects the approximate impact of the problem on the public health. This has been illustrated by two Tables in a paper by E.L. Anderson et al. (2) (Tables 4 and 5).

The rapid progress of research on the biological effects of chemicals results in quick expansion of the list of carcinogens. Making the legally binding decisions on

public health, based on qualitatively differing evidence that a given substance produces cancer in humans or only in animals, depends on the adopted classification and on the assignment of the substance to a given class. There are quite serious

Table 4. Upper-limit lifetime cancer risk for arsenic exposure[a,b]

Source	Number exposed in highest two groups[c]	Two highest exposure levels ($\times 10^{-4}$ mg/kg/day)[d]	Associated lifetime upper-bound cancer risk	Upper-bound estimates/cases per year
Copper smelters	43.800	2.7 – 1.5	$2 - 1 \times 10^{-3}$	1.5 – 0.821
Lead smelters	3.400	0.69 – 0.26	$6 - 2 \times 10^{-4}$	0.029 – 0.017
Zinc smelters	37.000	0.69 – 0.27	$6 - 2 \times 10^{-4}$	0.32 – 0.13
Cotton gins	3.2	15.4 – 6.9	$13 - 6 \times 10^{-3}$	0.0061 – 0.0027
Pesticide manufacturing	1.480	0.026 – 0.014	$2 - 1 \times 10^{-5}$	0.004 – 0.00025
Glass manufacturing	11.580	0.69 – 0.014	$6 - 2 \times 10^{-4}$	0.099 – 0.040

a) According to US EPA, Carcinogen Assessment Group, Assessment of risk associated with exposure to arsenic. May 2, 1980, National Technical Information Service, PB81 – 2006012.
b) The presented significant figures lack both precision and consistency, they are included merely to facillitate reconstruction of their derivation by means of various extrapolations and methematiclal calculations.
c)) Population exposed to communal arsenic levels according to the indicated exposure sources.
d) E.G. the highest exposure level for copper smelting is 2.7×10^{-4} mg/kg/day.

Table 5. Comparison of upper-bound risks associated with ambient exposure to carcinogenic air pollutants[a]

Chemical[b]	Upper-bound lifetime probablity of cancer death due to average exposure near stationary sources[c]	Total number exposed[c,e]	Total number of cancer deaths/year at the upper bound in U.S. due to chemical in air[c]
Arsenic	4×10^{-5}	25 million	16
Benzene	3×10^{-3}	220 million	78
Coke ovens	7×10^{-4}	15 million	150
Vinyl chloride[d]			
Before regulation	2×10^{-4}	5 million	20
After regulation	1×10^{-5}	5 million	1

a) From the US Environmental Protection Agency, Carcinogen Assessment, Group reports 1976 – 1981. These estimates may change as additional data become available.
b) All risk are before regulations unless otherwise indicated.
c) The significant figures presented do not indicate precision or accuracy, but are included to make it easier to trace the derivation of these numbers through the various extrapolation and mathematical calculations.
d) If risks were based on the incidence of mammary tumors in the bioassay studies, the results would be four times higher.
e) Population exposed to ambient levels of chemical listed. Exposure is from stationary air sources.

differences in the classifications adopted by various countries. The problem has been discussed in the first part of this work, which deals with the history of the exposure limits development. The differences in the classification of carcinogens, particularly the differences in assigning of some substances to a specified class, may suggest that they result not only from decisions on the matter or from the differences in opinions, but also from the political decision in which the economic consequences are taken into account.

In the documents prepared by US EPA which contain health evaluations of particular chemicals studied by the Agency, the index of carcinogenic potency, expressed in risk units, is specified in addition to the relative risk estimates. This enables comparing the carcinogenic potency of particular chemicals of proven carcinogenic action. The risk unit estimate is the increased individual lifetime risk for 70-kg person who breathes air containing 1μg/m^3 of the chemical during the person's lifetime, i.e. 70 years. For drinking water, this is 1μg/1 water. It is to be noticed that the risk units for air and water are in most cases quantitatively incomparable, since the daily air intake for an adult is approx 20 m^3, while for water the corresponding value is approx 2 liters. The values would be comparable only if the retention of the chemical in lungs amounted to 10%. This does not present a serious problem, since uncertainties attributable to extrapolation of the doses and evaluation of the results are likely to produce much greater differences.

It is also worth noting that the carcinogenic potential index expressed in risk units may differ by as much as million times. For such well known carcinogens as benzene or vinyl chloride, the calculated risk units are as high as 10^{-6}. It may be, therefore, concluded that the weight of evidence of substance carcinogenicity is not associated with its specified carcinogenic potential.

The presented survey of the questions associated with the derivation of hygienic standards for non-threshold agents does not cover all aspects of the problem. This has been due to the necessity of reaching a reasonable compromise.

The methodological fragments presented in this chapter are, in the author's opinion, necessary to undestand the derivation of the recommended limits and hygienic standards.

Finally, it should be noted that there is a noticeable difference between the quantitative risk assessment and risk management. Risk assessment determines the consequences of human exposure to a toxic agent. Risk management is the process of taking steps to eliminate the identified risk, or to reduce the risk to a level which is regarded, usually by some governmental public health agency, to be acceptable (17).

In occupational health practice of many countries (e.g. the U.S.A.) there is a noticeable boundary between risk assessment and risk management in the sense that the risk assessment is performed by the agencies or institutions associated with the ministry of health, while the risk management is carried out by the agencies subordinated to the ministry of labor, or by the ministry of labor itself.

In the environmental protection, risk assessment and risk management are usually concentrated at the same place, usually at a governmental agency dealing with environment protection (problems) (e.g. US EPA). Due to possible significant differences in the quantitative risk assessment, depending on the choice of data and on the employed mathematical models – the question always remains whether the supplied relative risk assessment product is useful and whether it will be correctly used in the risk management process. A reference to the controversies on that question has been already made in the text of the present work. Certainly, this question is difficult to be answered conclusively, e.g. because the numerical risk assessments cannot be considered to be final. As such decisions are taken by the authorized teams or persons, in addition to relevant competence they should be provided with the full documentation containing the health criteria and the methods of deriving risk assessment, together with all doubts which might affect final risk assessment during the particular stages of the procedure.

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