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EPA Proposed Guidelines for Carcinogen Risk Assessment

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BEFORE THE ENVIRONMENTAL PROTECTION AGENCY

COMMENTS OF THE

EUROPEAN CHEMICAL INDUSTRY ECOLOGY AND TOXICOLOGY CENTRE

(E C E T O C)

ON

EPA PROPOSED GUIDELINES FOR CARCINOGEN RISK ASSESSMENT

(49FR 46294, November 23, 1984)

Pursuant to the instruction given in the Federal Register of 23 November, 1984, please accept the attached written comments from ECETOC (The European Chemical Industry Ecology and Toxicology Centre) on the Environmental Protection Agency's Proposed Guidelines for Carcinogen Risk Assessment which were published in the Federal Register as above.

ECETOC is a non-profit making international association of 41 companies who operate in West Europe, and are engaged in the industrial manufacture of chemicals and research in this field.

ECETOC was formed to :

a) procure all types of information relevant to the protection of the health of any person who may come into contact with chemicals and to reduce the ecological impact of the manufacture, processing and use of chemicals;
b) coordinate efforts by chemical manufacturers to study and attempt to resolve the ecological and toxicological problems which may result from the manufacture, processing and use of chemicals;
c) cooperate in a scientific context with government, health authorities and all other public institutions concerned with ecological and toxicological problems relating to chemicals.

Commercial questions are excluded from the objectives and concerns of the Centre.

A. INTRODUCTION

Members of ECETOC have a vital interest in the promulgation of good guidelines for carcinogen risk assessment and therefore appointed a group of responsible practicing scientists from member companies to draw up comments on the EPA's proposals. This group comprised :

Dr. I. Purchase, Director of Imperial Chemical Industries' Central Toxicology Laboratory.

Dr. B. Broecker, Coordinator for Product-related Environmental Problems, Hoechst.

Dr. E. Loeser, Toxicology Department, Bayer.

Dr. R. Jaeckh, Toxicology Department, BASF

Dr. W. Tordoir, Head of Occupational Health and Toxicology Division, Shell Internationale Petroleum My.

The comments have been approved by ECETOC's senior scientific body, its Scientific Committee, whose membership is given in the attachment.

B. COMMENTS

As a general statement of philosophy, the proposed guidelines are a substantial step forward in regulatory thinking about the control of carcinogens. The separation of hazard identification and risk assessment (dose reponse assessment, exposure assessment and risk characterisation) from risk management allows the proper scientific evaluation of the carcinogenicity data without the social and political pressures inherent in the risk management process. In its publication on carcinogen risk assessment ECETOC (1980) recommended the separation of the overall carcinogen risk assessment into the above three steps. A key consideration in ECETOC's report on which many of the following comments are based is incorporated in the statement "Uncertainties in the risk estimation process should not lead to either over- or under-estimation of risk, as either could act against the best interests of society". Central to the ECETOC position is the belief that the scientific evaluation of carcinogenicity should provide as accurate an assessment of risk as is possible and should also indicate the assumptions and variability inherent in the assessment. The provision of such data is a pre-requisite for making sensible regulatory decisions and for an understanding by the general public of the magnitude of any likely risk. This position regarding the need for accurate risk assessment has also been proposed by the US Presidential Task Force on Regulatory Relief (US, 1983). In their "Regulatory Policy Guidelines", p.19, item 4 they state that "Regulations that seek to reduce health or safety risks should be based upon scientific risk-assessment procedures, and should address risks that are real and significant rather than hypothetical or remote" and on p.32 that "To be useful in determining overall benefits and costs, risk assessments must be scientifically objective and include all relevant information. In particular, risk assessments must be unbiased best estimates, not hypothetical "worst cases" or "best cases". Extreme "best" or "worst" safety or health results should be weighted (along with intermediate results) by the

probability of their occurrence to estimate the expected result implied by the available evidence. In addition, the distribution of probabilities for various possible results should be presented separately, so as to allow for an explicit "margin of safety" in final decisions."

The recommendations from ECETOC, together with the supporting reasons for them, are given below.

1. Short-term Tests (Section II.B.5)

Recommendation : This section should read "Tests for point mutations, numerical and structural chromosome abberations, DNA damage/repair/binding studies and in vitro transformations which have been adequately validated for predicting carcinogenicity are used as screening tests for carcinogenicity. They may provide supporting evidence of carcinogenicity and information on potential carcinogenic mechanisms. A range of properly-validated tests for each of the above end-points helps to characterise the spectrum of response of a carcinogenic agent. On their own, data from these tests cannot be used for risk assessment".

The paragraph "Short-term in vivo .... evidence for carcinogenicity" should be deleted.

There are over a hundred assays which can be considered as candidates for short-term tests for carcinogenicity. Many have only a tenuous link to carcinogenicity, i.e. they have a mutation end-point. Others are based on assay systems which have such major differences from whole-animal studies that they are not relevant to the induction of cancer by chemicals. This subject has been reviewed recently by The International Commission For The Protection Against Environmental Mutagens and Carcinogens (ICPEMC, 1982) who have provided evidence concerning those tests, from amongst the hundred or so candidates, for which there is evidence of validation. Regulatory guidelines should provide some perspective which will enable a selection of appropriate test systems for regulatory purposes.

The results of short-term tests for initiation and promotion activity cannot be used as supporting evidence of carcinogenicity because the scientific data on which these tests are founded are far too meagre at

present. They are, however, useful in providing an understanding of the mechanism of action.

2. Results from Studies which Provide Data that are Inappropriate for Human Risk Assessment (Section II.B.6.).

Recommendation: For chemicals which induce "mouse-liver-only" tumours, or certain others in the mouse such as lung, and some lymphoid, tumours, the animal carcinogenicity evidence is appropriately assessed as "limited evidence".

The results from certain experimental test systems are not relevant to human risk assessment because consideration of the mechanism involved indicates that the process is not likely to, or does not, occur in man. There are several test results which fall into this category including, (a) the occurrence of bladder tumours in the presence of bladder stones, (b) the induction of injection-site sarcomas, (c) an increase in the incidence of certain tumours which have a high incidence in rodent models, with ancillary information indicating that the response is specific to rodents. In all of these examples the experimental model is inadequate and hence the data should be assessed as "inadequate evidence".

Good evidence has now been collected that a number of chemicals which produce a "mouse-liver only" tumour response are not carcinogenic in man. The same applies to certain other types of tumour such as "mouse-lung-only" tumours and some types of lymphoma in the mouse. The proposed guidelines acknowledge the widely-diverging scientific views on the validity of these tumour responses but in spite of this they place too much reliance on "mouse-liver-only" tumours in the classification scheme. These results may well be reproducible in mice, and even between strains of mice, and therefore cannot be considered as spurious - in other words they may be considered as sufficient evidence of a carcinogenic response in mice. There is growing evidence, however, that it is inappropriate to classify these chemicals with respect to carcinogenicity in man, in contrast to the situation when classification is based on unequivocal results from animal experiments.

It is particularly inappropriate to classify a chemical as carcinogenic when conditions such as the following are met : the response observed in the mice is only at toxic dose levels and/or only at the end of the study; no substantial dose-related increase in the proportion of malignant tumours occurs; the occurrence of tumours is predominantly benign, showing no evidence of metastasis or invasion; no dose-related shortening of the time to the appearance of tumours is observed; the occurence of the excess tumours is only in a single sex and the results from a spectrum of short-term tests is negative. The need to take into account the impact of chronic tissue damage in the affected organ must also be emphasised : if dose levels are so high that they produce such damage, the resulting increases in tumour incidence are not relevant to the carcinogenic risk to humans when tissue damage does not occur. The above types of evidence should be assessed as "inadequate evidence".

The understanding of the mechanisms by which subcutaneous injections produce local tumours in rodents, and the way in which bladder stones induce bladder cancer, also indicates that these responses are irrelevant to the assessment of risk to humans. Reponses of this sort should therefore be assessed as "inadequate evidence".

3. Negative Epidemiological Evidence (Section II.B.7)

Recommendation : Negative epidemiological studies should be used to calculate the upper bound of risk and this estimate of risk should be included in the summary of risk characterisation (Section III.C.3). Good negative epidemiological data should also be used in the categorisation of overall evidence, particularly in groups B.II and C.

Epidemiological studies provide the only evidence which is directly relevant to man. The guidelines suffer from the major shortcoming that they ignore negative epidemiological evidence, presumably because "negative results from such studies cannot prove the absence of carcinogenic action". ECETOC recognises that it is impossible to prove the absence of a carcinogenic effect by an epidemiological study. However, the EPA system is based on weight of evidence and in our view too much weight is given to evidence from inadequate animal carcinogenicity studies, at the expense of negative epidemiological studies, in the

categories B.II and C. As the quality of epidemiological studies improves with the incorporation of good exposure estimates, so their validity in the risk assessment process increases in comparison to unvalidated observations from inadequate animal carcinogenicity studies.

4. Quantitative Risk Assessment for Agents in Group C (Appendix IV, C, Group C,c)

Recommendation : Quantitative risk assessment should be used for agents in group C only where there is a definitive malignant tumour response in a single well-conducted experiment.

Usually, most of the data which will result in the classification of a chemical in group C, "possible human carcinogen", will be from studies which do not exclude chance, bias or confounding factors, and such data should not be used for any quantitative risk assessment.

5. Pooled Estimates of Risk (Section III.A.1)

Recommendation : In this Section, which deals with two or more significantly-elevated tumour types, the recommendation that pooled estimates will generally be used in preference to risk estimates based on single sites or types should be deleted.

We see no justification for adding together the different types of tumours for which there are statistical increases. To take this procedure to its logical conclusion, any tumour type which shows a statistical deviation from the controls should be included in the summation. This implies that tumours which decrease with respect to dose should also be included. There is evidence that the dose-response relationships for different tumour types produced by the carcinogen in the same experiment differ widely, eg. for acetylamino fluorene (AFF) in the EDO_1 study (Gaylor, 1980), and methyl butyl nitrosamine. There can be no scientific justification for simple summation of these responses. The summation of different tumour types may lead to a risk estimate lower or higher than the highest risk calculated for a specific statistically-increased tumour type alone. For these reasons we see no justification for the proposal to pool estimates.

6. Assumptions Inherent in the Mathematical Extrapolation Models (Section III.A.2)

Recommendation : In the statement on the choice of mathematical extrapolation models, the assumptions which are inherent in the use of the models should be given. When the statement on the risk assessment of an individual chemical is prepared, the summary of risk characterisation (Section III.C.3) should provide an explicit account of the assumptions inherent in the process of risk characterisation.

In its Monograph No.2, ECETOC (1980) stated that "With putative and questionable human chemical carcinogens, the quantitative estimation of the carcinogenic potential is a difficult task because no adequate human data are available and qualitative information is incomplete. Two specific difficulties usually arise. Firstly, there is the gap between the observed effect of high doses in animal models and the non-observed effects of low doses which may be more relevant to human exposure. Secondly, there are the gaps between experimental models and man. Once it has been demonstrated that the extrapolations across these gaps are qualitatively feasible (which is not often the case, and certainly not in some in vitro methods), by taking into consideration all available data, including appropriate negative human data - a fundamental step that is frequently ignored - quantitative approaches have been used. While mathematical models are very useful for understanding experimental systems, they are not valid for quantitative extrapolation from one species to another or from one exposure condition to a different one".

The major assumptions which are usually made in the use of mathematical extrapolation models occur in the extrapolation from high to low doses and from animals to man. In the case of extrapolation from high to low doses, the assumptions are : (a) that the selection of a mathematical model is arbitrary as it cannot be based on goodness-of-fit to the observable data, nor on mechanistic considerations; (b) that the shape of the dose-respnse curve in the area of importance, namely at low doses, is unknown, but that a linear dose-response curve is selected because it provides a worst case estimate; (c) that the pharmacokinetics and metabolism remain constant with respect to dose over the whole dose range studied; (d) that, unlike the situation for virtually all other biological phenomena, there is no

known threshold; and (e) that even where there is a likelihood of determining a threshold - in the case of non-genotoxic carcinogens - a mathematical model which does not include thresholds is used. In the second step of the extrapolation process the following assumptions are usually made : (a) that the animal responds in an equivalent fashion to man; (b) that the metabolism and pharmacokinetics of the chemical are the same in the experimental animals as in man; (c) that the lifetime of the experimental animals is considered as equivalent to that of man; (d) that the dose administered to the experimental animal is exactly the same as a numerically-equivalent dose in man, apart from some crude corrections for differences in the ratio of body weight to body surface area.

7. Evidence for Linearity at Low Dose (Section III.A.2)

Recommendation : In the choice of mathematical extrapolation models, the preference given to linearity at low dose should be replaced by a more balanced selection of models which includes those which assume linearity at low dose, those which assume non-linearity at low dose, and those which allow for thresholds. The selection of a mathematical model should take into account whatever information is available about mechanism of action. In particular, for non-genotoxic carcinogens there is no evidence to support the use of linear extrapolation models and the extrapolation to low doses should establish a threshold, or use models which incorporate a threshold. In all cases the estimate of risk should be based on the most scientifically-acceptable assumptions and should provide an indication of sensitivity, for example by including upper and lower confidence limits.

We agree with the opening sentence in Section III.A.2 that risks at low exposure levels cannot be measured directly either by animal experiments or by epidemiological studies. All of the available experimental data are at relatively high doses where it might be possible to conclude that the added effect of a carcinogen or a tumour initiator is virtually linear. We do not believe that it is possible to conclude that this is so at low doses and therefore it is not logical to base all mathematical extrapolation on the untestable hypothesis that the dose-response at low doses is linear. At this stage of the science it is recommended that

other types of mathematical extrapolation should also be used to cover other possible dose-response relationships.

As indicated in the introduction to this document, ECETOC believes that the best interests of society are served by providing as accurate an assessment of risk as is possible, and that over- or under-estimation of risk is scientifically indefensible. If it is important to be conservative in the regulatory control of carcinogens, this conservatism should be explicitly stated at the risk management stage and should not result in biased estimates of risk.

Numerical point-estimates of risk give an idea of spurious accuracy to the unitiated lay or scientific reader. The production of risk estimates to only one significant figure only partly rectifies this problem. There are adequate mathematical techniques for estimating the sensitivity or reliability of risk estimates, and in all other fields of science statements about reliability and reproductibility of estimates are included. We believe that low-dose risk estimation is no exception.

8. Equivalent Exposure Units Among Species (Section III.A.3)

Recommendation : The approach to making inter-species comparisons of dose should be characterised by the same flexibility of choice, supported by reasons, which applies to other parts of the guidelines.

Whilst there is evidence that for some toxic or pharmacological responses the power of 0.67 applied to body weight can be used to transfer dose-response relationships between species, there is no evidence that such a treatment is generally applicable to carcinogens. The power relationship is unlikely to be universal. For directly-acting carcinogens which do not require metabolic activation and hence are detoxified by metabolic activity, the appropriate extrapolation from animals to man is on the basis of mg per m^2 of body surface area, ie. body weight to the power 0.67. However, for chemicals which are metabolically activated to proximate carcinogens the reciprocal of this conversion factor is appropriate because the relative amounts of activated metabolites in plasma and tissues are lower in larger species (Rietz et al., 1978). The relative carcinogenic potencies of such chemicals in rats and mice

correlate well with their relative metabolic rates in these species (Greim et al., 1981).

Extrapolations carried out as above are conservative because they do not take account of the more effective DNA repair which occurs in longer-lived species such as man. It is recommended that even if direct evidence of comparative metabolism and pharmacokinetics is lacking, a general knowledge of the metabolism of the class of chemical by the species, and the possible mechanism of carcinogenicity, be considered before the means of transferring dose-responses between species is chosen.

9. It is Incorrect to Pro-Rate Daily Exposure over a Lifetime (Section III.B)

Recommendation : The method used to pro-rate results from long-term experiments to short-term exposure should take into account knowledge of dose/time/response relationships in chemical carcinogenicity. In particular, the pro-rating of time should be to a power of at least two.

On page 46299, first column, the guidelines state that "Unless there is evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as average daily exposure pro-rated over a life-time, is recommended as the appropriate measure of exposure to a carcinogen. That is, the assumption is made that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over a lifetime". There is good experimental evidence to show that this assumption is incorrect. Druckrey (1967), who studied the incidence of tumours induced by a variety of carcinogens, concluded that for a particular carcinogen the product of dose (d), and time (t) to a power (n), remained constant. He expressed this in the form of the equation, $d \times t^n = k$. For the majority of carcinogens studied the value of n is between 2 and 4. If the statement in the guidelines is to be true, the value of n would always have to be 1. There is no published evidence to suggest that any dose-response curve for a carcinogen leads to that value.

A second point to be taken into account is that for many chemicals the rate of metabolism is not linear with dose. Thus the work of Ghering et al. (1977) has demonstrated unequivocally that the metabolism of vinyl

chloride becomes saturated at high doses, and that the proportionate amount of active metabolite produced at high doses is smaller than at low doses. The same is true for a multitude of other chemicals which have been studied in this way, including , e.g. chlorinated solvents and nitrobenzenes. Additional evidence is provided by experimental data on nitrosamine carcinogenesis where the organ specificity changes with dose (for example methylbutylnitrosamine produces oesophageal cancer at high doses but liver cancer at low doses). If the production of proximate carcinogens is not linearly related to dose over the whole dose range in a particular exposure situation, it is incorrect to assume that d x t = k for both high and low doses. There is direct experimental evidence from animal studies to show that this assumption is incorrect. The administration of a given dose of aflatoxin to rats produces a different tumour response depending on whether the dose is given as a single administration, or as multiple administrations the sum of which are the same as the dose given in the single administration. Similar results have recently been reported for epichlorhydrin (Laskin, Sellacombe et al., 1980).

This suggests that it would be extremely unwise to base regulatory decisions on simple pro-rating, as suggested in the guidelines, when there is clear evidence that it is incorrect.

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for ECETOC

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