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A Contribution to the Strategy for the Indentification and Control of Occupational Carcinogens

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A CONTRIBUTION TO THE STRATEGY FOR THE IDENTIFICATION AND CONTROL OF OCCUPATIONAL CARCINOGENS

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FOREWORD

It is with pleasure that I introduce the second Monograph from ECETOC, the European Chemical Industry Ecology and Toxicology Centre.

The potential carcinogenicity of chemicals is of concern to the chemical industry, the regulatory authorities and the public. To deal effectively with this problem a well-defined view of its scientific basis is essential — indeed it is the only basis upon which a successful identification and control of potential chemical carcinogens can be established.

The chemical industry has made significant contributions to the development of methods for identifying and controlling carcinogens. In Western Europe a number of companies have toxicological research laboratories staffed with experts, whilst many other companies have staff experienced in carcinogenicity testing carried out for them in contract laboratories. Moreover, there is considerable experience in the practical day-to-day issues involved in identifying and controlling carcinogens. The great majority of these companies are members of ECETOC and it is not surprising that, after its formation in 1978, members felt strongly that its considerable scientific resources should be used to clarify views about the complicated topic of carcinogenicity. A Task Force of experts was therefore selected and started work in April 1979.

The Monograph represents the first phase of the Task Force's work and indicates both the determination and commitment of the chemical industry to broaden its knowledge in this field in which it has a significant responsibility for the protection of its employees and the general public. This responsibility is shared with the regulatory authorities and I hope that this Monograph, by providing an objective and scientific analysis of this complex topic, will assist them in the very difficult task of developing legislation which will confer the maximum benefit to society.

I can best conclude by quoting the Monograph directly :

« ... 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.»

A. ROBERTSON
Director, Imperial Chemical Industries Limited
Chairman, ECETOC

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SUMMARY

This monograph deals with issues and principles which are key contributors to the strategy of identifying and controlling chemical carcinogens. Cancer is a disease with special characteristics and therefore the criteria for its control are somewhat different from those adopted for the control of other types of toxic risk. Irrespective of the contribution that industrial chemicals make to the total environmental causes of cancer, both government and industry have to make serious attempts to control exposure which results in occupational cancer. In dealing with this complex topic it is essential to start from as clear a scientific basis as is possible.

A critical assessment is first made of the techniques used (epidemiology, animal tests and short-term tests) to identify the carcinogenic potential of chemicals, and the nature and limitations of the scientific evidence derived from these techniques are discussed. From an expert interpretation of this evidence, chemicals may be classified as **proven, putative** or **questionable human carcinogens,** and **human chemical non-carcinogens.** This classification step is part of the process of assessing carcinogenic potential and should be followed by further steps including quantification of the risk according to the circumstances of actual human exposure. Decisions on whether this quantified risk is acceptable is one to which scientists contribute, but should involve a broader contribution from other members of society. The assessment of carcinogenic risk is too complex a subject for simple generic rules to be laid down, and expert judgement of the evidence is required in each case.

In the judgement of the carcinogenic potential of a chemical, evidence from short-term tests often plays an important role. This evidence is only qualitative (yes-no), and the conditions necessary to give a high degree of certainty that the qualitative result is correct are discussed. Only when these conditions are met, can decisions based on short-term test results be made.

A. INTRODUCTION

1. SCOPE AND PURPOSE OF THE MONOGRAPH

The causes of most types of cancer are not known and the mechanisms by which cancer develops are complex and equally imperfectly understood. It is known, however: that certain chemical substances do produce cancer in man by a variety of mechanisms which may differ from substance to substance. Because of this absence of a clear knowledge of the cause of cancer, there are many differing views as to how cancer should be controlled and there is continuing disagreement about the strategy for its prevention.

In an attempt to control the production and use of chemical carcinogens, legislation has been passed in many countries governing the use of chemicals as pharmaceuticals, pesticides or food additives, which requires the testing of these chemicals for carcinogenicity prior to marketing. Legislation is also in existence in many advanced industrialised societies for the control of occupational carcinogens. In these initiatives for the control of occupational carcinogens there are many differences in approach which reflect different perceptions of the knowledge in the field of cancer research and the different socio-economic circumstances in the various countries enacting the legislation. These differences may serve to emphasise the fact that there is no clear and easy way of controlling chemical carcinogens.

In this Monograph the major means of identifying carcinogens are outlined and some of the reasons why each of these alone is inadequate are discussed. A discussion of these features indicates the complexity of the subject and leads to the conclusion that there is no alternative to sound scientific judgement of the evidence existing for each individual chemical concerned.

Within the whole topic of the identification and control of occupational carcinogens, there are certain important issues and principles which, although they are controversial, are nevertheless the key to the whole strategy of control. These have been addressed in some detail in this Monograph.

2. SPECIAL STATUS OF CANCER AS A DISEASE

Of all the diseases known to man, cancer has come to occupy a special place in the concern of people living in industrially developed societies during the past decades. Cancer is much more frequent today than it was in the last century because people are living longer. As hygiene and medicine have improved, the mortality from infectious diseases has decreased and life-expectancy has increased. A larger proportion of the population is therefore of old people and they are the ones who predominantly die from cancer.

Cancer is a life-threatening disease and in most cases, there is no effective cure. It often has a long latency and there are usually no symptoms or signs of the disease which develop at an early enough stage to give an opportunity for effective curative treatment. Hence, prevention of cancer cannot be based on observations of those at risk without a significant number of them actually developing cancer.

For these reasons, criteria for the control of carcinogenic substances are somewhat different from those for the control of other risks from exposure to chemicals, although the general principles of risk assessment are the same.

3. ENVIRONMENTALLY-CAUSED CANCER AND THE CONTRIBUTION OF SYNTHETIC CHEMICALS

There are large variations in the incidence of cancer between different groups of people. These variations can be explained either by differences in the genetic make-up of the people, or by differences in the environment in which they live. Studies of migrant populations moving from one country to another have indicated that the predominant factor is in fact environmental since the populations which migrate gradually develop the cancer pattern of the country to which they migrate. This has led to the suggestion that the major proportion — about 80 % — of cancer is attributable to environmental factors. At first sight this appears to be a relatively simple concept but it has nevertheless been the subject of much controversy. This may be because environmental concern has become linked with concern for pollution and the activities of the chemical industry. Hence, the attribution of 80 % of cancers to the environment has been taken to indicate that the chemical industry has contributed a large amount to that incidence of cancer. The high and variable incidence of cancer in non-industrialised societies leads to the conclusion, however, that environmental factors, which include life-style and tobacco smoking, must be considered on a much broader base.

There is already good evidence that cigarette smoking, sunlight and life-style make the major contribution to the incidence of cancer. According to J. Higginson, founding director of the World Health Organisation's International Agency for Research on Cancer (IARC), less than 6 % of the total incidence of cancer may be attributed to occupational exposure.

TABLE 1

Proportion of cancer in man which can attributed to various factors (See Science 205, 1363, 1979)

Factors contributing to the incidence of cancer	Percentage of cancers in	
	females	males
a) Environmental *		
Tobacco	7	30
Tobacco and alcohol	3	5
Sunlight	10	10
Occupation	2	6
Radiation	1	1
Iatrogenic	1	1
Life-style	63	30
b) Non-environmental		
Congenital	2	2
c) Unknown	11	15

* Environmental factors are those which are not endogenous to humans, but are related to their habits and the surroundings in which they live and work.

Even if the majority of cancer is caused by environmental factors other than synthetic chemicals, there still remains the problem of occupationally-caused cancer. The acrimony in the debate about the relative contribution of various environmental factors to cancer cannot obscure the fact that occupational cancer does occur. Irrespective of the arguments about the contribution of synthetic chemicals, natural products and radiation to occupational cancer, society demands of governments and industry that they make serious attempts to control the exposure which results in occupational cancer.

4. TECHNIQUES USED IN THE IDENTIFICATION OF CARCINOGENIC POTENTIAL

There are three basic techniques leading to the identification of carcinogenic potential, namely, epidemiology, animal studies and short-term predictive tests for carcinogenic activity. In each case there are strengths and limitations of the techniques.

4.1 Epidemiology

The use of epidemiology where observations are made on people exposed to chemicals is the only method which provides unequivocal evidence of human carcinogenicity. Epidemiological techniques are time-consuming and difficult to carry out, and to date only approximately 30 chemicals or occupations have been identified as producing human cancer. The technique can be applied only to chemicals which have been in use for an adequate period of time, and when this reveals an increased incidence of cancer the opportunity of preventing cancer induction has already been lost.

To be an effective tool in the identification of occupational cancer, the observations in man have to be linked very closely to information on exposure or occupation over the whole of the latency period for the appearance of cancer, which may be up to 40 years. Historically, records are very poor and in practice quantitative records are rare and only qualitative records of exposure are available. This often puts limitations on the way in which data of the epidemiological studies can be interpreted. Frequently the sizes of groups at risk in industrial situations are so small that only very potent carcinogenic effects or very unusual neoplasms can be detected. As cancer from non-occupational causes is so common, it is always necessary to compare the incidence of cancer in exposed groups to that in control populations. This in itself is affected by a number of confounding factors, such as the difference in cancer incidence by social class and geographical region.

These sorts of difficulties lead to the conclusion that the precision of most epidemiological studies is not high, but although there are some problems in interpretation they remain an essential method for evaluating the carcinogenicity of chemicals already in use.

4.2 Laboratory models

For very obvious reasons, epidemiology cannot be the only means of identifying carcinogenic potential. In situations before human exposure has occurred or when epidemiology is impossible for other reasons, predictive tests based on laboratory models are the only means available for identifying carcinogenic potential.

4.2.1. Long-term animal studies

One of the major advantages of long-term animal studies for detecting carcinogenic activity is that exposure is defined and controllable. The life-span of the commonly-used laboratory animals is shorter than that of man and hence the latency period is also shorter. Adequately designed long-term animal studies have the advantage that they are the closest model to the human situation, as it is known that many neoplasms in animals have similar morphological and behavioural characteristics to those observed in man.

As in the use of all model systems, the major problem associated with their use is that the design has to compromise between what is desirable and what is feasible. One critical factor is having sufficient confidence in a negative result from an animal carcinogenicity study. If there is a 10 % incidence of a particular cancer in the control group, very large numbers of animals need to be used in order to detect a doubling of the cancer incidence (Table 2).

TABLE 2

The number of animals per group required to give a 90 % chance of detecting certain increases in incidence, when the control group has a 10 % incidence, and using a significance level of ≤ 0.05.

Increase in incidence to	No. of animals per group
80 %	12
60 %	21
40 %	46
20 %	255
15 %	826

Thus, even enormous experiments by present-day standards can only detect changes in incidence of a relatively large size (say 10 or 20 %). Increases in cancer incidence of that size in the human population would usually be considered unacceptable. In order to overcome or compensate for the difference between the sizes of experiments that can reasonably be carried out, and the size of populations at risk, much larger doses of the chemical than those to which man would be exposed are administered to the experimental animals. This in turn poses the problem that often the extremely large doses induce systemic or tissue-specific toxicity, distort the homeostasis in the animal, and provide results which are even more difficult to interpret and extrapolate to the human situation.

Other features of design which require critical, scientific judgement include the influence of environmental factors (such as temperature, humidity and light) ; the influence of diet and route of administration ; the selection of dose, species, strains, sex ; and many other factors. Finally, although the time taken for the execution of a long-term animal study is very much shorter that the elapsed time before a reasonable epidemiological study can be carried out, it is still a substantial period (up to three or four years) and the costs are high.

Even though long-term animal studies provide the closest model we have to the human situation, the extrapolation of results from animal studies to man is extremely difficult. It is possible to get some idea of the reliability of prediction of carcinogenicity by comparing the results of carcinogenicity tests in two laboratory animal species. Table 3 shows that there is approximately an 85 % probability that a chemical carcinogenic in one species will also be carcinogenic in the second species. The differences are often the result of differences in metabolism. Whether this accuracy of prediction also occurs between animal species and man is not known. It seems likely that the accuracy of prediction between rodent species and man would be worse than the accuracy of prediction between two rodent species.

TABLE 3

The sensitivity and specificity of results from carcinogenicity studies in rats and mice, and vice versa [1].

	Sensitivity [2] %	Specificity [3] %
Rat studies	84	85
Mouse studies	82	82

1 The figures are calculated from the results of carcinogenicity studies on 250 chemicals reported in the literature.

2 Sensitivity : the proportion of positive results in one species for those chemicals found positive in the second species.

3 Specificity: the proportion of negative results in one species for those chemicals found negative in the second species.

4.2.2. Short-term tests for carcinogenicity

Because of the high cost and resource-requirements of long-term animal studies, and the length of time required for results to be obtained, there has been a move to develop tests which cost less and provide results after a shorter period. Most of these tests are based on the observation of mutagenic action of test substances on cells in culture. Some are also based on observations of effects of chemicals on the growth pattern of mammalian cells, the so-called cell transformation test. There is such a large variety of these test systems available that it is not possible to describe each one of them in detail in a brief monograph of this kind.

The utility of short-term tests for carcinogenicity depends largely on the empirical correlations which have been obtained between results from the short-term tests and observations of carcinogenicity in mammalian species. A variety of such validation studies has shown that results from the Salmonella microsome-plate incorporation assay (the so-called Ames test) correlate well with animal carcinogenicity studies. Sensitivity and specificity values of around 90 % have been obtained in various laboratories. Only some of the other available short-term tests, such as those using E. coli as the indicator organism, point-mutation systems in eukaryotic cells, and cell transformation have achieved similar sensitivity and specificity figures.

The main advantage of tests of this type is, of course, the rapidity and cheapness of the testing. In addition, some information on the mechanism of action may be obtained. The limitations of these tests come from the fact that they are extremely simple models for the rather complex interaction which occurs in man. In particular, the simplified metabolic systems which are present in the **in vitro** tests may not reflect the pharmacokinetics of, and the complete range of metabolic options which are available in, a whole animal. Attempts have been made recently to examine whether there is a correlation between the potency of action in short-term tests and the potency of the carcinogenic action in animal studies. It appears at this stage that this correlation is not sufficiently well understood for a quantitative extrapolation of results from short-term tests to be considered acceptable.

It is now well recognised that both false positive and false negative results occur, a feature which must be taken into account when interpreting the results from screening programmes.

B. ECETOC PROPOSALS

1. DEFINITION AND CLASSIFICATION OF CHEMICAL CARCINOGENS

Consideration of definitions prepared by other groups leads to the view that the definitions are only relevant to very carefully specified circumstances. Many of the definitions lose their relevance when they are applied to the everyday problems of controlling the manufacture and use of chemicals. It is thus necessary to understand the need for such definitions which are primarily to assist scientists from regulatory bodies and industry to assess the carcinogenic potential of chemicals for man. In order to do this it is necessary clearly to differentiate between **carcinogenic potential** and **carcinogenic risk.**

The word «potential» means «capable of coming into being or action». and **carcinogenic potential** (not to be confused with potency) is thus a property that a chemical possesses which will enable it to produce a carcinogenic effect under appropriate conditions. This concept should be clearly differentiated from **carcinogenic risk**, which is the probability that a certain population exposed to the chemical under specified conditions of dose, duration and route of exposure will develop an increased incidence of cancer.

1.1. Carcinogenic potential

Etymologically the word «carcinogen» means «causing cancer». In common use, cancer is a general term for all forms of malignant neoplastic growth which have the characteristic feature of autonomous multiplication of cells, without the normal growth regulation, somewhere in the body. From a cell behavioural and morphological viewpoint, malignant neoplasia is characterised by the invasion of cells into neighbouring tissues or organs, metastasis, and with certain histomorphological criteria.

Many chemicals are incapable themselves of producing cancer but, when metabolised by enzymes in the animal tissues, produce reactive chemical species, known as proximate carcinogens, which are believed to interact with critical cellular components. Thus, terms such as procarcinogen, ultimate carcinogen and proximate carcinogen are used to describe the various stages in the metabolic modification of the carcinogen. These subdivisions are not further taken into account because, as has been stated earlier, the purpose of these definitions is to assist in the assessment of carcinogenic potential in man, and because the definitions are concerned only with those chemicals to which man is exposed.

The carcinogenic potential of any chemical can be revealed only by appropriate observations of its effects on humans or on suitable experimental systems. As these date accumulate, a clearer view of the carcinogenic potential of the chemical is revealed.

There are many chemicals for which evidence of carcinogenicity in humans or experimental systems is absent, or so incomplete, as to defy classification. For some chemicals, opinion based on information other than that derived from human or specific experimental studies on carcinogenicity supports the likelihood of human carcinogenic potential. For others, however, there is insufficient evidence to allow classification which is meaningful in terms of controlling human exposure. The inability to classify chemicals because of paucity of data, or the classification as «questionable» or «putative» is considered provisional until such time as sufficient data are available for a clear classification.

On the basis of these considerations the following definitions may be made. These definitions, which provide a uniform basis for classification, are essential for risk assessment but form only a part of it :

1.2. Proven human chemical carcinogen :

«A proven human chemical carcinogen is a substance for which a causal relationship has been established between previous exposure and the occurrence of malignant neoplasms in man».

1.3. Putative human chemical carcinogen :

«A putative human chemical carcinogen is a clearly-defined chemical substance which causes malignant neoplasms in adequate animal experimentation, under exposure conditions which correspond to those in man, or where the relevance of the exposure conditions can be deduced».

1.4 Questionable human chemical carcinogen :

«A questionable human chemical carcinogen is a clearly-defined chemical substance for which there is incomplete evidence of carcinogenicity, which is based either on (a) observations in man which are suggestive, but do not allow a firm conclusion of a causal relationship between previous exposure and the occurrence of malignant neoplasms ; or (b) findings obtained in animal experiments in which the experimental model is not appropriate to conditions in man and therefore the result cannot be regarded as relevant ; or (c) positive findings in at least two standardised short-term tests, with unrelated end-points, which have been verified as useful for screening for carcinogenic potential».

1.5. Human chemical non-carcinogen

«An ultimate proof of non-carcinogenicity is impossible. However, a clearly-defined chemical substance which has consistently shown negative results in adequate studies in man or adequate animal experimentation should be considered a «Human chemical non-carcinogen» for practical purposes».

2. CONCLUSIONS BASED ON SHORT-TERM TESTS FOR CARCINOGENICITY WHEN PART OF A REGULATORY BASE SET

Most toxicological information is quantitative, and the majority of the information in, for example, the EEC proposed toxicological base-set is no exception. Thus, for example, the reporting of acute oral or dermal toxicity is given as an LD_{50} expressed as a numerical value of dose per unit body weight. One notable exception to this rule is short-term testing for mutagenicity (see Appendix A) or carcinogenicity. There are in fact very good scientific reasons, e.g. quantitative and qualitative differences in metabolism, for not using data from short-term tests for a numerical quantification of mutagenic and/or carcinogenic **risk** in man. Such data are relevant to assessing carcinogenic **potential.**

The consequence is that the qualitative nature of the result (either positive or negative) puts particular emphasis on its accuracy. It is not possible to calculate the probability of error of a result expressed only as «positive» or «negative». This emphasises the need for a high degree of certainty that the qualitative result is correct, so that subsequent decisions are made on a sound footing.

In considering what decisions should be taken on the basis of a positive or a negative short-term test, the first and most important step is to establish that the result is «confirmed». There are several conditions which must be met before a result can be considered confirmed, and one of the most important is that the result from a second short-term test should be in agreement (see below). Carcinogenic or non-carcinogenic activity is suggested only when this and the other conditions are met.

Special problems, which are not yet resolved, are presented by mixtures and thus results from the testing of mixtures should be regarded with caution.

2.1. Requirements for a «confirmed» result

For the result of testing a chemical in short-term tests to be considered «confirmed», it must meet the following criteria :

2.1.1. The result should be derived from a test carried out to a protocol meeting minimum criteria (i.e. the protocol should be supported by a formal validation study) **or** the «chemical class control pairs» should have performed as expected in the same experiment. (A «chemical class control pair» is defined as a pair of chemicals, both structurally-related to the chemical under test, one of which is carcinogenic and the other non-carcinogenic).

2.1.2. The result should be the same in two test systems with unrelated end-points.

2.1.3. The result should be consistent with the experimental design, e.g. there should be a clear dose-response relationship ; where no increase in colonies is seen in a bacterial mutation test, it should be established that this is not due to high toxicity ; in a bacterial mutation test, an increase in colony counts should be confirmed by replicate plating

2.1.4 The positive controls used to check the reliability of the test should be used in parallel with each experiment.

2.1.5. The result should be reproducible if performed at different times in separate laboratories.

2.1.6. An assessment should be made of the likely contribution of impurities to the test result. Impurities which are strongly positive in the test system or highly toxic to the test organism can lead to incorrect results.

2.2. An unconfirmed result

If any one of the above criteria is not met, the result becomes an unconfirmed result.

2.3. Consequences of a confirmed positive result

Since there are sufficient controls and checks in the experiments leading to a confirmed result, it has certain characteristics, namely it is reproducible ; it is consistent with the known response of the tests to that chemical class ; each test is shown to have been performing accurately at the time of the experiment ; the chemical itself is responsible for the result ; and the result is the same in two tests. These controls and checks provide a result which is the best possible indication of carcinogenicity short of actually carrying out an animal carcinogenicity study, although it falls short of proof of carcinogenicity. If any one of the criteria for regarding a result as confirmed is not met, it should be considered an **unconfirmed result.**

2.4. Consequences of a confirmed negative result

In the absence of other relevant toxicological data, a confirmed negative result from short-term tests is a good indication of non-carcinogenicity. However, other considerations, eg. the size of the exposed population and the likely dose absorbed, may make it prudent to carry out additional testing in whole animal systems.

2.5. Consequences of an unconfirmed result

There are many occasions when the result is unconfirmed eg. if it is positive in only one test, or if the results are not fully reproducible. An unconfirmed result is a temporary situation and generally needs further studies in order to confirm the positive result or to obtain a confirmed negative result. If the result remains unconfirmed, then expert judgement regarding the significance of the unconfirmed result is required when it is used, with all the other factors available, as one element in the process of the risk assessment. Whatever decision is taken, it should be reviewed when new information becomes available and the result becomes confirmed.

The data produced by short-term tests can be considered as part of the process of identifying carcinogenic potential. Other points (including chemical and toxicological properties and exposure conditions), have to be taken into account for risk assessment and, thus, the decisions taken must be based on a consideration of all the data for each chemical and situation.

C. CARCINOGENIC RISK ASSESSMENT - BASIC CONCEPTS

The approach to the assessment of risk from carcinogenic chemicals is frequently over-simplified. There is a great danger of equating carcinogenic potential with carcinogenic risk. Scientists involved in regulation and in industry, and all those concerned with the decision-making surrounding chemical carcinogens, need to be fully aware of the multistage process of risk assessment and recognise their respective contribution to each stage. As this is such a complex topic, only some basic principles are presented in this section.

A three-step assessment procedure is recommended :

1. Risk Identification

The first step in risk assessment is to identify chemicals by classifying them, using all available evidence, according to the definitions given above.

Such classes would include :

a) proven human chemical carcinogens
b) putative human chemical carcinogens
c) questionable human chemical carcinogens
d) human chemical non-carcinogens.

In the case of some chemicals there will be insufficient evidence to allow classification.

2. Quantitative Risk Estimation

The concept of numerical quantification of carcinogenic risk implies a precision of prediction that does not exist. Even with proven human chemical carcinogens, quantitative risk estimation is only relatively straightforward when the duration and intensity of exposure are known.

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 effects of high doses in animal models and the non-observed effects at 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.

Having established the anticipated carcinogenic potential of the substance in man (hazard assessment), risk quantification should then take into consideration the complex circumstances of actual human exposure (exposure assessment). Potential and risk are different concepts. Risk is the likelihood that the potential of the substance to induce cancers in man is expressed under particular conditions of exposure. Many factors, including the inherent carcinogenic potential, will determine whether or not cancer will ensue from exposure. In the industrial context, these include the physical properties of the compound (e.g. dustiness, volatility and solubility), the process involved (e.g. batch or continuous process), the equipment in which the operation is to be carried out, e.g. (open or closed system), and the protective measures that are, or can be, taken during the periods of possible contamination. For chemicals in the environment and for consumer uses involving large numbers of people exposed to low concentrations, it is crucial to have reliable estimates of actual or anticipated exposure levels

There may be additional factors which influence the risk quantification and which have to be considered separately, e.g. increased susceptibility of certain identifiable human sub-groups.

3. Risk Evaluation

When a panel of experienced scientists has carried out the risk identification and quantification, the acceptability of the risk to society is the next crucial point. This involves: the ranking of the anticipated cancer risk on a scale of other recognised risks and balancing it against society's willingness to accept the risk ; social benefits ; economic cost of control of exposure ; and available technology and alternatives. Indeed the wish to maintain its vital interests or standard of living may influence society in its decisions as to which risks should be run and at what level.

This three-step process of risk assessment does not allow a generic approach and each substance must be evaluated separately. Even for single substances, owing to the complexity of the process the estimate of risk can be only approximate. The assessment is based on current information available from various test systems and the current scientific assessment of their validity.

As new information becomes available, a reassessment should therefore be carried out in order to improve the estimate. Nevertheless, these 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.

D. CONCLUSIONS

The evaluation of carcinogenic potential and the process of risk assessment is a complex and contentious subject. Our knowledge of the processes which cause cancer and lead to its development is not well advanced, and is insufficient for simple rules to be laid down against which an assessment of carcinogenic risk can be made.

Until more is known about the causes and development of cancer there is no substitute for recognising that cancer has a special place in people's concern and requires different criteria for judgements of acceptability of risk than is the case for other risks. Prior to a judgement of the acceptability of risk, the risk assessment should comprise two other stages, namely the identification of carcinogenic potential and the quantification of the risk. Expert judgement from scientists and others involved in the regulatory process is required on each and every case to ensure that the risk is controlled in a satisfactory and economical fashion.

APPENDIX A : DEFINITION OF A MUTAGEN

The ECETOC Task Force on Carcinogenicity has developed the following definition of a mutagen :

«A mutagenic substance is a clearly-defined chemical which can generate a mutation in a particular cell or organism.

A mutation is the result of an interaction of the substance with genetic material leading to a change of genetic information which can be passed from parent to progeny (from cell to cell and/or from organism to organism)».

In principle the definition of mutagenicity is applicable to organisms from all phyla. Hence, although all organisms have DNA in common as the basis for hereditary processes, its organisation and the enzymes responsible for repairing DNA damage differ, for example, from prokaryote to eukaryote. The metabolism and distribution of chemicals in **in vitro** tests may differ considerably from those observed **in vivo.** It is necessary in reporting a mutagenic activity of chemicals to include information on the indicator organism and the concentration of the chemical which produces a minimum detectable effect.

Indicator organisms and their environmental conditions are frequently grossly modified in order to enhance artificially the sensitivity of the test. Chemically-induced mutations in short-term tests or **in vivo** experiments on animals do not necessarily indicate a mutagenic hazard to man.

APPENDIX B : MEMBERS OF ECETOC TASK FORCE CARCINOGENICITY

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APPENDIX C : MEMBERS OF ECETOC SCIENTIFIC COMMITTEE

J. RUTSCHMANN	(Chairman) Director responsible for Environmental Protection, Safety and Quality Assurance	SANDOZ (Basel)
A. RODEYNS	(Vice-Chairman) Coordinator, Environmental Protection and Product Safety	SOLVAY (Brussels)
H. ZELLER	(Vice-Chairman) Head of Dept. Industrial Hygiene and Toxicology	BASF (Ludwigshafen)
J. BACKSTROM	Consultant Toxicologist	ASSOCIATION OF SWEDISH CHEMICAL INDUSTRIES (Stockholm)
B. BROECKER	Coordinator, Product-related Environmental Problems	HOECHST (Frankfurt)
H.O. ESSER	Vice Director, Agrochimie Division	CIBA-GEIGY (Basel)
K.W. JAGER	Manager, Group Toxicology Division	SHELL (Den Haag)
U. KORALLUS	Medical Director	BAYER (Leverkusen)
R. MATTIUSSI	Responsible for Medicine and Industrial Hygiene	MONTEDISON (Milano)
H.G. NOSLER	Head, Coord. Centre for Consumer Safety and Environmental Protection	HENKEL (Düsseldorf)
A.A.B. SWAN	Director, Central Toxicology Laboratory	ICI (Alderley Park)
C. de TORREGROSA NAVARO	Director of Medical Services	UNION EXPLOSIVOS RIO TINTO (Madrid)
J. VERRIER	Director of Industrial Toxicological and Eco-toxicological Service	RHONE POULENC (Paris)
H VERSCHUUREN	Toxicology & Registration Dept.	DOW CHEMICAL (Rotterdam)