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# Assessment of the Risk of Exposure to Chemical Carcinogens

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***ABSTRACT*** *: The methods used for risk assessment from exposure to chemicals are well established. In most cases where toxicity other than carcinogenesis is being considered, the standard method relies on establishing the No Observed Adverse Effect Level (NOAEL) in the most sensitive animal toxicity study and using an appropriate safety factor (SF) to determine the exposure which would be associated with an acceptable risk. For carcinogens a different approach is used because it has been argued there is no threshold of effect. Thus mathematical equations are used to extrapolate from the high doses used in animal experiments. These methods have been strongly criticised in recent years on several grounds. The most cogent criticisms are a) the equations are not based on a thorough understanding of the mechanisms of carcinogenesis and b) the outcome of a risk assessment based on such models varies more as a consequence of changes to the assumptions and equation used than it does from the data derived from carcinogenicity experiments. Other criticisms include the absence of any measure of the variance on the risk assessment and the selection of default values that are very conservative. Recent advances in the application of risk assessment emphasise that measures of both the exposure and the hazard should be considered as a distribution of values. The outcome of such a risk assessment provides an estimate of the distribution of the risks.*

***Key Words*** *: Carcinogen, Risk assessment, Threshold, Genotoxic, Mechanism*

## 1. Purpose and principles of risk assessment

The inherent toxicity of chemicals varies by up to 100,000,000-fold and the exposure of individuals varies by a similarly large factor. Decisions aimed at controlling the adverse effects of chemicals must take account of these large differences in both toxicity and exposures in order to optimise the improvement in human or environmental health at an affordable cost. Decisions taken *only* on the potency of the toxic events or *only* on exposure levels are unlikely to control the adverse effects of chemicals because both are equally important. It is for this reason that risk assessment has become such an important component of national and international regulation of chemicals.

Assessment of the risk of exposure to chemicals is based on the same steps whether the chemicals are carcinogenic or have other toxic properties. Thus, there is an important distinction between hazard and risk, which are defined as:

- *Hazard*: Set of inherent properties of a substance, or mixture of substances, that under production, usage or disposal conditions make it capable of causing adverse effects to organisms or the environment depending on the degree of exposure; in other words it is a source of danger.
- *Risk*: Possibility that a harmful event arising from exposure to a chemical or physical agent may occur under specific conditions, or the expected frequency of occurrence of a harmful event arising from exposure to a chemical or physical agent under specific conditions.

In all cases of risk assessment there is a stepwise process which takes account of both the hazard and the exposure of the chemical under study in order to assess the magnitude of the risk. The details of this process differ with different organisations, but the outcome is the same-either the assessment of the magnitude of risk under particular circumstances of exposure or the setting of standards to protect human health or the environment.

## 2. The distinction between carcinogens and non-carcinogens for the purpose of risk assessment

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The problem that faces those carrying out risk assessment of genotoxic carcinogens is how to determine the likely cancer incidence at environmental doses often a million times less than the doses necessary to induce cancer in animal experiments.

Since the early work demonstrating the importance of somatic mutation as a critical step in chemical carcinogenesis, the ability of carcinogens to cause mutations is considered to be an integral part of the mechanism by which they induce cancer. This culminated in the paper by Ames and co-workers (Ames *et al.*, 1975) with the title 'Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection'. It was believed that all carcinogens acted via mutagenesis and that to detect a mutagen was equivalent to detecting a carcinogen.

The mechanism for chemically induced mutation, where co-valent binding of the chemical to DNA is the first step, lends itself to the idea that a single molecule is sufficient to cause an irreversible mutation. In turn this has lead to the concept that carcinogens act via a mechanism which has no threshold. Put in another context, this means that some believe there is no safe dose of a chemical carcinogen, because even a single molecule can induce a critical mutation.

The contrast with non-carcinogenic chemical toxicity lies in the idea that most types of toxicity do have thresholds, defined as doses below which the toxic event does not occur. This is most easily seen in the case of chemicals, such as vitamin A, which is a necessary component of food but can be toxic at higher doses (causing foetal abnormalities when pregnant women take a sufficient dose, some 5 times the necessary dose). Hence risk assessment of toxic chemicals relies on the concept of a threshold for toxicity. The method of choice relies on identifying a No Observed Adverse Effect Level in animal toxicity studies and applying an appropriate Safety Factor. The safety factor is often a factor of 100, being a 10-fold factor to take account of inter-species differences and a 10-fold factor to take account of differences in individual susceptibility. Larger or smaller factors can be used when the circumstances dictate.

### 3. Genotoxic and non-genotoxic carcinogens

Since the important publication by Ames and his colleagues, knowledge of the mechanisms by which chemicals cause cancer has developed rapidly. The first observation to challenge the assertion that all carcinogens are mutagens was the study of the mutagenicity of those chemicals tested and found to be carcinogenic in the US National Toxicology Programme. Work by Ashby and Tennant (1991) demonstrated that the mutagenicity of chemicals found to be carcinogenic in tests using rats and mice differed depending on the extent of carcinogenic response. Thus, a high proportion of chemicals found to be carcinogenic in both rats and mice and in multiple organs were mutagenic (70%). However, for carcinogens affecting only one site in one species, the proportion found to be mutagenic was much lower (34%). Thus only a proportion of even the most effective carcinogens were mutagenic. An explanation other than mutation was needed for the mechanism of carcinogenicity of those chemicals causing cancer in only one organ in one species.

In parallel with these observations, a considerable research effort was directed at establishing the mechanisms responsible for these cancers. It is now clear that the mechanisms responsible for inducing cancer by non-genotoxic chemicals are often specific to the organ in which the cancer occurs. Thus, thyroid and kidney cancers in rats can be induced by mechanisms specific and to those organs in rats. The high doses used in traditional carcinogenicity studies also contributed to the number of chemicals found to have these species-specific cancers. There are many more examples of these non-genotoxic carcinogens (Purchase, 1991). The mechanisms identified include:- Hormone-receptor-mediated mechanisms, cytotoxic effects and other alterations to normal physiology. In most cases, the chemical is now known to affect either cell division or cell death (apoptosis) or both in the target organ.

For these non-genotoxic carcinogens, it is clear that the paradigm used for risk assessment of other (genotoxic) carcinogens is inappropriate. As there is no evidence that non-genotoxic chemicals interact directly with DNA, a non-threshold approach to risk assessment is inappropriate. Thus in most countries, the NOAEL-SF approach is used successfully for non-genotoxic carcinogens.

### 4. Approaches to genotoxic carcinogen risk assessment

Concerns about the effect of carcinogens at low doses have lead to the use of 'mathematical models' to extrapolate from high experimental doses to the lower doses experienced in the majority of environmental exposures. In these methods the incidence of cancer in the groups of animals exposed to the chemical is used as the starting point and the likely incidence at the expected exposure is calculated. In most of the mathematical equations used, the relationship between dose and incidence of cancer is linear or nearly linear. Other factors may also be taken into account to deal with the differences in body mass and physiology between animals and humans.

The most widely used method is the linearised multi-stage model that was in use by the US EPA for many years. Because of the uncertainties in this form of extrapolation, the 95% upper confidence limit of the estimate of cancer incidence was used for risk assessment purposes.

In 1998, proposals were introduced to change the assessment process. The model used now relies on an estimate of the dose required to induce a 10% incidence of cancer. This figure was chosen because it is within the experimental region and the errors from extrapolation are minimised. A strictly linear extrapolation from this point in the dose-response curve is then made. Once again, the 95% lower confidence limit of the dose is used for the estimation of the dose at 10% incidence. (Note that the 95% upper confidence limit of the incidence is equivalent to the 95% lower confidence limit of the dose.) The advantage of this method is that the strictly linear low dose extrapolation is easier to visualise and understand.

Other countries, such as the UK, use a more pragmatic approach to risk assessment of genotoxic carcinogens. It can be described as the comparative risk approach. An assessment of the carcinogenicity of the chemical and its dose response is carried out and this is compared to the likely exposure level. Pragmatic measures are taken to reduce the exposure to as low as is possible, with emphasis being placed on situations where there is only a relatively small margin of safety between the experimental carcinogenic doses and the likely exposure.

## 5. The question of reliability and accuracy of carcinogen risk assessment

One of the main concerns about the methods that rely on mathematical equations for extrapolation to low doses is that there are no methods to confirm their accuracy. In one or two cases it has been found that the incidence of cancer in exposed populations is far less than might be expected if the linearised extrapolation method is applied. But probably the most worrying aspect of these methods is that the result of the extrapolation depends as much on the mathematical equation used as it does on the experimental carcinogenicity data. Thus, by changing the model from linearised to probit or logit, the estimate of risk can change by as much as 5 orders of magnitude.

A further concern arises from the use of the 95% upper confidence limit for estimation of risk. The consequence is that even relatively large changes in the experimental data have little or no effect on the final estimate of risk. A much more important influence on the estimate of risk is the highest dose given in the experiment. This is worrying, because so much effort is put into ensuring that the reported results of carcinogenicity studies are accurate; if that information does not have much influence on the outcome of the risk assessment it suggests a flaw in the methodology.

The ultimate purpose of risk assessment is to inform those who are exposed to the risk and those who are responsible for assessing the risk. We have shown that the 2 methods of risk assessment currently in use (NOAEL/SF and linearised multi-stage modelling) provide conflicting messages to those to whom the information is given (Purchase and Slovic, 1999). Thus, by using two methods for risk assessment we are failing in meeting the principle measure of success of the overall process, namely that those involved in risk management are properly informed.

## 6. Recent developments and their impact on the risk assessment process

*Mechanisms.* Recently, Lutz and Kopp-Schneider (1999) reported the results of modelling the effects of carcinogens on the dose response for tumour induction. Their hypothesis is that effect of low-level DNA damage is to delay the cell cycle resulting in a reduction in the 'spontaneous' tumour incidence; at higher cytotoxic doses of the carcinogen there is an accelera-

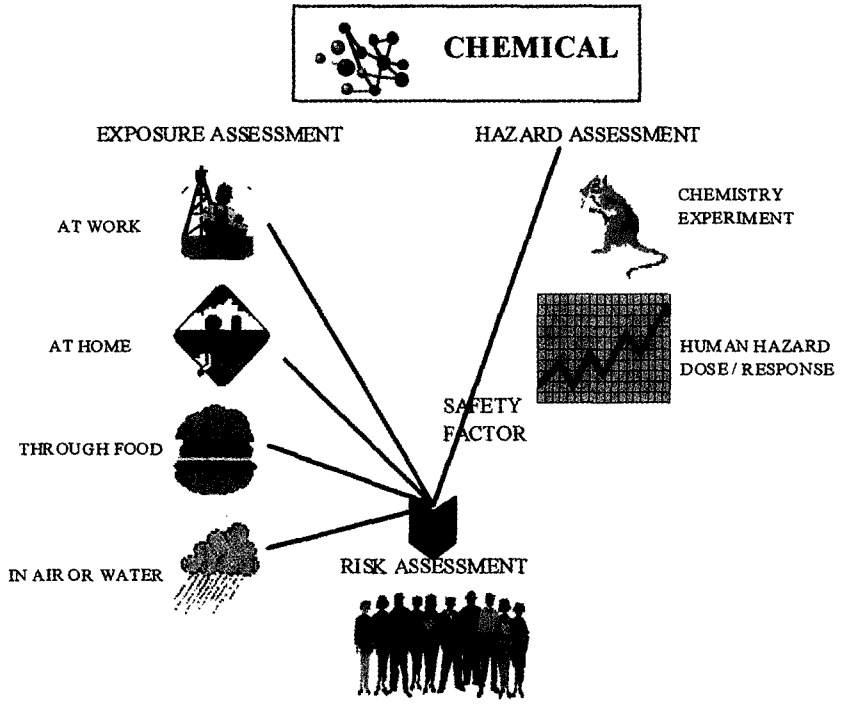


**Fig. 1.** Current paradigm for risk assessment. The risk is assessed for the population based on exposure derived from various routes and assessment of hazard for the 'average' member of the population. A safety factor (usually of 10) is applied to allow for variations in human susceptibility.

tion of cell cycle leading to an increase in tumour incidence. This U-shaped dose response curve allows the presence of a threshold for a genotoxic carcinogen.

These observations are of great importance to risk assessment in that they may allow a reconciliation of the two risk assessment methods.

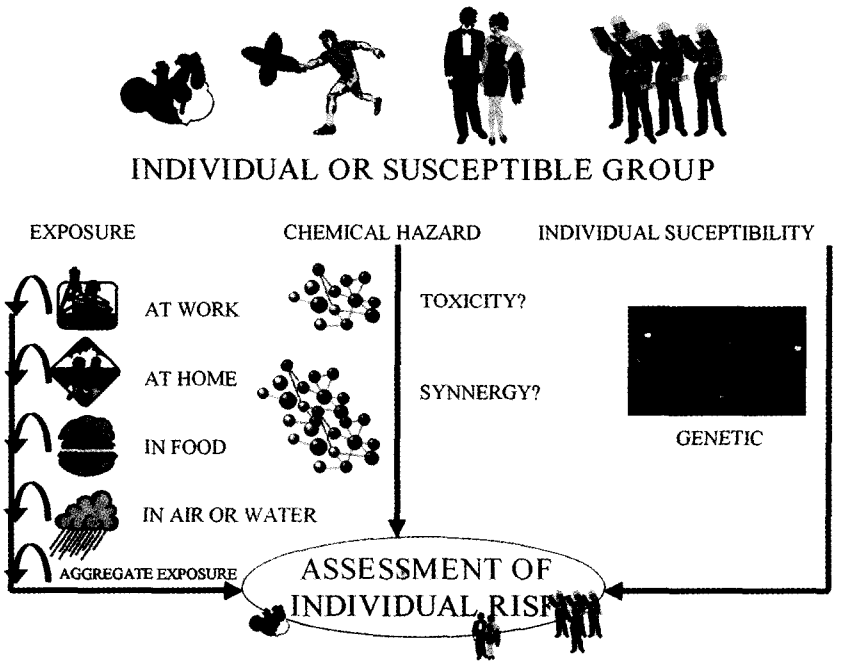


**Fig. 2.** Future possibilities for risk assessment. The risk of exposure could be assessed for individuals (or particular susceptible groups) from knowledge of individual exposure and individual susceptibility.

*Probabilistic approaches to risk assessment.* For many years estimates of exposure expressed as a single value and safety factors also expressed as a single value have been used in risk assessment. Exposure assessment can now be carried out in a much more meaningful way, with distributions of exposure used in risk assessment instead of using the 'maximally exposed individual' (Paustenbach, 2000). Similarly, Renwick and Lazarus (1998) have shown that variability in human susceptibility can be modelled. Through their work a clearer idea of the effectiveness of the safety factors used in risk assessment is now available. In future, hazard, expsoure and safety factors may be expressed as distributions, providing the opportunity to assess risk for the whole population or sub-populations with greater accuracy.

*Genomics.* The ability to study the effects of chemicals directly on genes has become a reality in the last few years. It is within our grasp to be able to assess risk for a single individual, based on the knowledge of his/her genetic make-up and a clear estimate of their exposure.

The impact that this might have on the approach to risk assessment is presented in Figs. 1 and 2. Currently risk assessment relies on an assessment of the human hazard using the 'average' human as a target; variations in susceptibility are taken into account by the use of a 'safety factor' (usually of 10, unless there is information to the contrary to cover inter-individual variation (Fig. 1). In future it may be possible to assess the risk for individuals because sophisticated methods of assessing individual genetic susceptibility and individual exposure (Fig. 2).

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