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Journal of Hazardous Materials 39 (1994) 143–148

JOURNAL OF HAZARDOUS MATERIALS

Issues in interpretation of toxicological data for use in risk assessment

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"Modest doubt is called the beacon of the wise", William Shakespeare

Abstract

Risk assessment models are most often based upon data obtained from animal bioassays. Not always; do those who perform the risk assessments question the validity of the carcinogenic experiment. The suggestion here is that animal data should be used for calculation of risks only when experiments employ routes that mimic human exposure: oral, inhalation, or dermal. Other issues that concern an experimentalist include the use of maximum tolerated dose. Also an issue is that it is impossible to "prove" a compound is safe, therefore all models must follow the concept that there is no threshold. Other issues are related to unusual results of bioassays, such as the induction of tumors in organs of animals with no human counterpart, and the claims of tumorigenisis in animals with a high spontaneous rate of tumors. The experimentalist suggests that risk assessment values be followed by a number which indicates a certainty factor, the range being 1–5. Number 1 indicates the data are robust, number 5 implies that the risk assessment value is at best determined by conjecture.

1. Introduction

The definitions and even the connotations of risk are well known. All approaches to *risk assessment* should expect that an estimate be made of the likelihood that a specific number of people will develop a certain disease following a known exposure to an agent or chemical. Until recently, the emphasis was on the relation of chemical exposure and cancer. Other pathological and abnormal conditions can also be associated with exposure to chemicals; these include congenital malformations. Some learning disabilities and lower IQ tests are also being associated with exposure to exogenous agents. This essay will be limited to the discussion of issues related to the application of quantitative risk assessment data to the cancer problem.

SSDI 0304-3894(94)00051-H

1.1. Available information on risk assessment

There is no dearth of books on risk assessment. After the first book by Lawrance [1] on this subject, almost ten others appeared [2–10]. Articles numbering many hundreds have also been published.

1.2. Factors considered in risk assessment

Mathematical models are presently used for quantitative carcinogenic risk assessments. As the art of the science advances, the mathematical models become more sophisticated; all of them attempt to estimate exposure at low levels from the data available at much higher levels. Different regulatory agencies may use different models and from the information given in the selected model, regulations on the maximum exposure are promulgated.

The numerical value given for cancer risk assessment (e.g., the potential number of cancers per 1,000,000 expected after exposure to a known concentration of a "carcinogen") is most often determined from experimental information, the relationship between the dose given to animals and the number of cancers induced. The major assumption is that it is possible to predict human carcinogenicity from animal studies [11]. A note and plea here is that the term "experimental carcinogens" should be used when a chemical induces a tumor in an animal model. More human information is needed before the generic term carcinogen, without a modifier, should be used. With the possible exception for an agent like arsenic, information from epidemiological studies alone would not be adequate for the calculations. Some useful information on the comparison of cancer development in humans from epidemiological studies and animal bioassays is published by Tomatis and Bartsch [12].

In reality, quantitative risk assessment is not based solely on "hard data". Involved in the decision can be consensus, individual personal assumptions, and even (official) policy [13]. For example, the selection of which mathematical curve to use to calculate a risk number can be a policy decision. It is well known that different risk models using the same input can differ in the risk number by magnitudes. Recently Gori [14] has even questioned if risk assessment is a science! Also, Gregory [15] has noted that models do not really tell us what we have to know regarding human carcinogens.

With some exceptions when calculations are made, these risk assessment values were based upon the *reported* number (or percentage) of tumors induced at the various dose levels of an administered chemical. Suggestions are made that as long as carcinogenic potency is invoked, the quantitative risk assessment may be less important [16].

Another concern in the interpretation of data is that it is often assumed that both males and females are equally susceptible to the same agent. However, this is not always the case [17]. On the other hand, this approach is used unless there is evidence to indicate otherwise.

2. Reliability of animal data

Very few articles on *quantitative risk assessment* question the validity of the animal data. It should be noted that the most realistic results can be obtained from experiments that mimic human exposure routes such as inhalation, feeding, drinking, or skin contact.

2.1. Generation of data from bioassays

Only valid animal experiments, as discussed by Furst [18] should be the bases for calculating risk assessment values. Factors to be considered include the specific agent under investigation, not derivatives nor chemically altered compounds. Also important are the species tested, the dose, and the route of administration. Exotic routes like implantation of platinum discs in the eye may lead to the induction of tumors, but these experiments, like subcutaneous implantation of metallic foils have no relevance to humans [19]. Risk assessments should not be considered when using data from these experiments. Purchase [20] has also elaborated on some issues in animal carcinogenic studies. Furst [21] has expanded on the problems, and lists some pitfalls in assessing risks from carcinogens. Huff [22] discussed design strategies and reviews the details of good animal experiments.

Much has been said about the objection or rationale for using the maximum tolerated dose (MTD). In many carcinogenic experiments, tumors are only found after administering the test agent at the MTD. Ames and Gold [23] claimed that about 50% of the positive experiments would not be so if less than the MTD were employed. Apostolou [24] justifies the use of MTD on the bases that if $\frac{1}{2}$ of the MTD is used, it is possible to miss carcinogens which may affect humans. McConnell [25] has stated that the main problem with the use of the MTD is the final interpretation relative to human carcinogenesis. Carr [26] has critiqued the use of MTD. He offers as an alternative "the highest sub-toxic dose that can be tolerated by test animals over a long period of time. . ." .

2.2. Issues to be considered

Assumptions about the carcinogenic process include the idea that there is no threshold for a carcinogen. A challenge to this assumption would require that some philosopher prove a negative. This is not possible, and in no way can one prove a compound "has no toxic action" and is *absolutely* safe. As a result, any graph used in a model must show that the very first increment of a given dose results in the induction of some tumors.

Other questions can be raised by an experimentalist. What is the justification that demands that in the equation which proposes a probability of a response, P(d):

$$P(d) = 1 - \exp(-a_0 + a_1 d + a_2 d^2 + \cdots)$$

that a must be equal or greater than 0 [27]. Must the worst case always be used which forces the value of a to be a positive number? Biotransformation mechanisms,

Table 1

Dose (of compound X) mg/kg	Number of thyroid tumors found	
	Males	Females
0	12	3
2	0.5	8
0.75	6	2
1.0	6	1
2.0	10	2
4.0	18	6
8.0	30	15

DNA-repair rates and multi-agent interactions can be invoked to show that a can be either 0, or can approximate 0.

How do those who perform quantitative risk assessment take into account the following hypothetical case: Groups of 50 male and 50 female rats were given an oral dose of compound X which was administered by gavage in an inert vehicle. Each individual dose was adjusted by the weight of the animals so that each rat received an equivalent amount of the compound based upon a mg/kg basis. Control animals were given only the vehicle. At 21 months, 90% of the animals were alive; they were all sacrificed and their thyroids were examined for tumors. From the necropsies the information recorded was shown in Table 1.

Should the initial decrease in the number of tumors with increasing dose be ignored? Must the graph of dose–response be a positive curve and omitting troughs? This will ignore the information about the first few dose levels in that the first increase of dose will decrease the number of tumors found. In reality, the decrease in the number of tumors at the first few dose levels, before the increase in the number of tumors as the dose increases, is a real phenomenon. Data of this nature were found after treating rats with ethylene thiourea.

There are many more questions an experimentalist can ask.

1. What is the value of a risk assessment model if the agent induces tumors by an exotic route? For example, the injection of either zinc or copper chloride in the testes of roosters or rats will produce teratomas.
2. Can a compound be a threat to a human if that compound induces only one type of tumor in only one organ in only one species?
3. If a compound has been tested many times and only 2–3% of the tests show that it is positive, should that compound be considered a human threat? Must the 90+ % negative tests be discounted?
4. Can a model help determine if the data show a false negative or a false positive?
5. Is there a real rationale for summing the number of malignant and benign tumors as a total number of growths?
6. If the background spontaneous tumor rate is high, what percentage above the background must be considered?

7. Can a mathematical model differentiate between a carcinogen, a cocarcinogen or even a promoter?

8. Can the risk assessor ever come to grips with the experimental observation of a threshold? Again, how should one deal with a "negative?"

3. Conclusions

Risk assessment should give an idea of the potential threat for developing a cancer after exposure to an agent. Those who deal with mathematical models should give an idea of how strong are the data from which they work; hence, how certain are the results?

4. Recommendations

It should be possible for the final risk numbers, i.e. 1×10^{-6}, be followed by another number (in parentheses) which is a certainty factor. These numbers can be 1–5, 1 being most certain, and 5 showing a great deal of uncertainty, but still giving an idea of the magnitude of the risk. Examples can be as follows:

1. If a few good epidemiological studies are available, and there are valid-positive data from at least two species which agree, the risk assessment values can be considered logical and realistic.

The same certainty factor can apply if a compound induces malignant cancer in animals in a high percentage of the tested animals, if given by more than one route in more than one species. This assumes that only animal data are available, and that no epidemiological studies have been made.

This should also be the case where there are a number of near flawless epidemiology studies, but no animal data are available.

2. If there are bioassay results from more than one study, but good epidemiological studies do not show an association of cancer induction with that agent, the value for risk assessment should be in class (2). The same category should be given if the epidemiology is good, but the agent does not induce cancer in experimental rodents.

3. The numerical values obtained from the risk assessment are weaker if the epidemiology is flawed and there are questions about the animal experiments.

4. The risk assessment values are very weak if one or two animal experiments are available, but the tumors were induced by the employment of some exotic route. The same certainty value should be given if a tumor is induced in an animal in an organ with no human counterpart. In this class should also be induction of kidney tumors in a rodent by a mechanism involving an *alpha*-2-micro globulin in a rat.

5. The values are extremely weak if the derived risk assessment values are only from information used by inference.

The final question asked by the experimenter is why do we not now use an uncertainty factor to augment the risk assessment number? For example (1) is strong, and (5) is very weak. One should be able to see the following: "The risk is 10^{-6} (3)."

This will tell one that there is a probability of 1/1,000,000 exposed persons having a chance to develop cancer – however, the certainty factor is not the highest possible.

Granted, the regulatory agencies may not be able to deal with this notion, but it is scientifically valid.

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