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Project Summary

Investigation of Cancer Risk Assessment Methods

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The major focus of this study is making quantitative comparisons of carcinogenic potency in animals and humans for 23 chemicals for which suitable animal and human data exist. These comparisons are based upon estimates of risk-related doses (RRDs) obtained from both animal and human data. An RRD represents the average daily dose per body weight of a chemical that would result in an extra cancer risk of 0.25. Animal data on these and 21 other chemicals of interest to the U.S. Environmental Protection Agency (EPA) and the Department of Defense (DOD) are coded into an animal data base that permits evaluation using different risk assessment approaches.

The full report is the result of a two-year study to examine the assumptions, other than those involving low-dose extrapolation, used in quantitative cancer risk assessment. The study was funded by the DOD (through an interagency transfer of funds to the EPA), the EPA, the Electric Power Research Institute and, in its latter stages, by the Risk Science Institute.

This Project Summary was developed by EPA's Office of Health and Environmental Assessment, Washington, DC, to announce key findings of the research project that is fully documented in four separate volumes of the same title (see Project Report ordering information at back).

Introduction

The full report is the result of a two-year study to examine the assumptions, other than those involving low-dose extrapolation, used in quantitative cancer risk assessment. The objectives of the study are:

1. To identify and express quantitatively uncertainties that are involved in the process of risk estimation, excluding the uncertainties in the low-dose extrapolation model;

2. To examine the impact of the different assumptions that are made in risk estimation;

3. To compare results calculated from human and animal data, including the identification of the assumptions that produce the best correlation of risk estimates between humans and animals; and

4. To develop guidelines for presenting a range of risk estimates based on different but scientifically acceptable assumptions or assumptions that have considerable backing in the scientific community.

These objectives are pursued using empirical methods in which carcinogenicity data for 44 chemicals are analyzed systematically in a variety of ways. Particular attention is placed on those 23 chemicals for which there exist data from both animal and human studies suitable for making quantitative comparisons.

Table 1 lists components of a quantitative risk assessment based upon animal data. Each component requires a decision on the part of the risk assessor for which there is no unique "correct" choice. Also listed in Table 1 are various

possible approaches to each component. The choices that a risk assessor makes for these components affect the resulting estimates of risk. The choices for these components therefore are related to the uncertainty in assessment of risk from animal data.

Objective 2 is pursued by making different risk estimates for the 44 chemicals in the study by systematically varying the approaches to the components listed in Table 1. Examination of the distributions of the changes in the estimates associated with different approaches to the various components permits the examination of the impact of the various approaches (assumptions). These distributions also relate to the uncertainties in the process of risk estimation, so this work also applies to Objective 1.

A major part of the study involves making comparisons between risk estimates derived from animal data and those derived from human data for those 23 chemicals for which suitable data exist for both animals and humans. This work addresses the question of whether correlations exist between animal and human data, and therefore is of fundamental importance to the scientific validity of quantitative risk assessment. The practice of making quantitative estimates of human risk from animal data is based upon the hypothesis (heretofore essentially untested) that such correlations do in fact exist. If quantitative correlations can be shown to exist, then these correlations can provide a stronger scientific basis for risk assessment. Further, evaluation of the correlations and determination of these approaches to the components listed in Table 1 that produce the best correlations can suggest better risk assessment methods and assist in evaluating and presenting the uncertainty in risk estimates derived using those methods, in accordance with Objectives 3 and 4.

Conclusions

The major focus of this study is making quantitative comparisons of carcinogenic potency in animals and humans for 23 chemicals for which suitable animal and human data exists. These comparisons are based upon estimates of "RRDs" obtained from both animal and human data. An RRD represents the average daily dose per body weight of a chemical that would result in an extra cancer risk of 0.25. Animal data on these and 21 other chemicals of interest to the EPA and the DOD are coded into an animal data base that permits evaluation using different risk assessment approaches.

The major findings of this study are as follows:

1. Animal and human RRDs are strongly correlated. The knowledge that this correlation exists betwee animal and human carcinogenicit data should strengthen the scien tific basis for cancer risk assess ment and cause increased confi dence to be placed in estimates o human cancer risk made fron animal data.

Table 1. *Approaches to Risk Assessment Components*

1 *Length of experiment*
- a. *Use data from any experiment but correct for short observation periods.*
- b. *Use data from experiments which last no less than 90% of the standard experimen length of the test animal.*

2. *Length of dosing*
- a. *Use data from any experiment, regardless of exposures duration*
- b. *Use data from experiments that expose animals to the test chemical no less than 80% of the standard experiment length.*

3. *Route of exposure*
- a. *Use data from experiments for which route of exposrue is most similar to that encounterec by humans.*
- b. *Use data from any experiment, regardless of route of exposure.*
- c. *Use data from experiments that exposed animals by gavage, inhalation, any oral route, or by the route most similar to that encountered by humans.*

4. *Units of dose assumed to give human-animal equivalence*
- a. *mg/kg body wt/day.*
- b. *ppm in diet.*
- c. *ppm in air.*
- d. *mg/kg body wt/lifetime.*
- e. *mg/m^2 surface area/day.*

5. *Calculations of average dose*
- a. *Doses expressed as average dose up to termination of experiment.*
- b. *Doses expressed as average dose over the first 80% of the experiment.*

6. *Animals to use in analysis*
- a. *Use all animals examined for the particular tumor type*
- b. *Use animals surviving just prior to discovery of the first tumor of the type chosen.*

7. *Malignancy status to consider*
- a. *Consider malignant tumors only.*
- b. *Consider both benign and malignant tumors.*

8. *Tumor type to use*
- a *Use combination of tumor types with significant dose-response.*
- b. *Use total tumor-bearing animals.*
- c. *Use response that occurs in humans.*
- d. *Use any individual response.*

9. *Combining data from males and females*
- a. *Use data from each sex within a study separately.*
- b. *Average the results of different sexes within a study.*

10. *Combining data from different studies*
- a. *Consider every study within a species separately*
- b. *Average the results of different studies within a species*

11. *Combining data from different species.*
- a. *Average results from all available species.*
- b. *Average results from mice and rats.*
- c. *Use data from a single, preselected species.*
- d. *Use all species separately.*

NOTE: Underline indicates approach used in base analysis (Analysis O).

2. In the majority of cases considered, analysis methods for bioassay data that utilize lower statistical confidence limits as predictors yield better predictions of human results than do the same methods using *maximum likelihood estimates.*

3. Analysis methods for animal data that utilize median lower bound RRDs determined from the ensemble of data for a chemical generally yield better predictions of human results than analyses that utilize minimum RRDs calculated from all the studies available.

4. Use of the "mg intake/kg body weight/day" (body weight) method for animal-to-human extrapolation generally causes RRDs estimated from animal and human data to correspond more closely than the other methods evaluated, including the "mg intake/m^2 surface area/day" (surface area) method.

5. The risk assessment approach for animal data that was intended to mimic that used by the EPA underestimates the RRDs (equivalent to overestimating human risk) obtained from the human data in this study by about an order of magnitude, on average. However, it should be understood that the risk assessment approaches implemented in this study are computer-automated and do not always utilize the same data or provide the same result as the EPA approach.

6. Reasonable risk analysis methods can be defined for the chemicals in this study that reduce the residual loss (roughly the average multiplicative factor by which the RRD predictors obtained from the animal data are inconsistent with the range of human RRDs consistent with the human data) to 1.7. This is not the same as saying that the predictors are accurate to within a factor of 1.7, because the estimated ranges of human RRDs that are consistent with the human data cover an order of magnitude or more for most chemicals.

7. It has been possible to identify a set of analysis methods using the median lower bound estimates that are most appropriate for extrapolating risk from animals to humans, given the current state of knowledge and data analysis. It is possible to use the information and results presented in this investigation to calculate ranges of risk estimates that are consistent with the data and also incorporate many uncertainties associated with the extrapolation procedure.

8. The many components of risk assessment are interrelated and evaluation of risk assessment methods should focus on the complete risk assessment process rather than on individual components.

9. The data base and method used in this study can provide a useful basis for evaluating various risk assessment methods.

This study only compared human and animal results for a relatively high risk level. It did not examine the uncertainty inherent in the low-dose extrapolation process.

The animal data base and the methods used in this study provide a useful basis for evaluating quantitative risk assessment. Their use in the present context has demonstrated the strong positive correlation between the animal and human risk estimates and, hence relevance of animal carcinogenicity experiments to human risk estimation. Moreover, it has been possible to identify methods of analysis of the bioassay data, including the choice of the median lower bound predictor, that satisfactorily predict risk-related doses in humans. Application of these methods has led to suggested guidelines concerning the prediction of human risks and the presentation of ranges of estimates incorporating the relevant uncertainties.

There are, however, certain features of this investigation that should be borne in mind when evaluating the results of this study. These are summarized below.

- A risk level of 0.25 is used throughout.
- The bioassay data is rather crude in several respects. The data deficiencies and their impact on the ability to perform some analyses are discussed in the document.
- The epidemiological data is of variable quality. Some degree of subjectivity is inherent in the estimates of uncertainty associated with the epidemiological RRDs.
- Different forms (complexes) of some chemicals were grouped together.
- Other approaches to the components could be defined and investigated.
- The three loss functions employed in the prediction analysis lack an underlying statistical development and so have been used merely to rank the analysis methods.
- Many other analysis methods could be investigated.

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The complete report consists of four volumes entitled "Investigation of Cancer Risk Assessment Methods:" (Set Order No. PB 88-127 097/AS; Cost: $80.00)

"Summary" (Order No. PB 88-127 105/AS; Cost: $14.95)

"Volume 1. Introduction and Epidemiology" (Order No. PB 88-127113/AS; Cost $32.95)

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