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Project Summary

Statistical Methods for Estimating Risk for Exposure Above the Reference Dose

A statistical method has been developed that provides a risk estimate for noncarcinogenic effects at a given dose. The method uses a categorical regression procedure to model severity of effect as it relates to experimental dose. Toxicity data are analyzed from multiple animal experiments that span different species, target organs, toxic effects, and exposure conditions. The data are screened for homogeneity with respect to experiment duration and route of exposure. The resulting dose-response curve provides an estimate of the risk of adverse effects that may be useful in estimating risk for exposures above the reference dose (RfD).

This Project Summary was developed by EPA's Environmental Criteria and Assessment Office, Cincinnati, OH, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

The U.S. Environmental Protection Agency (U.S. EPA) is charged with the responsibility of protecting public health from environmental pollutants. In this capacity, the U.S. EPA establishes a reference dose (RfD) for noncancer toxicity of individual chemicals (U.S. EPA, 1988; Barnes and Dourson, 1988). The U.S. EPA's formal definition of the RfD is:

> "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime."

The determination for the RfD for a given chemical involves several judgmental steps. First, the literature on its toxic effects is evaluated. The most scientifically sound study with the most appropriate NOAEL (no-observed-adverse-effect level) of the critical effect is then generally chosen, and that NOAEL is divided by uncertainty factors to arrive at the RfD. To date, there has been much concern regarding the risk of adverse effects for exposures above the RfD, but no reliable method for estimating this risk has been developed.

The evaluation of toxicity data for noncarcinogens is complicated by the multiplicity of possible endpoints, and the variation both in the severity of effect and in the response rate. Standard dose-response models most often assume a fixed severity (e.g., lethal) and endpoint (e.g., cancer), and would then need to be generalized into a multivariate form to be applicable to noncarcinogenic effects. Since response rates for noncarcinogenic effects are rarely reported, multivariate dose-response models are seldom developed, and "dose-response" analysis usually relates dose only to the severity of the observed effects. The approach presented here assigns the severity descriptions to ordered categories and

models the "dose-category" relationship. Modeling the risk of adverse effects using categorical regression was proposed previously (Hertzberg and Miller, 1985; Hertzberg, 1987), but the statistical algorithm then used was limited.

Results and Conclusions

Several different computer programs and groupings of the data have been investigated in order to find the best approach for applying categorical regression to this dose-severity modeling. Much progress has been made: available data were put in a form conducive to such an analysis, a model was selected, a statistical algorithm was found to perform the analysis, ways of presenting the results were explored, some goodness-of-fit measures were evaluated, and a mainframe programming package was written to perform the analysis. For this document, a logistic transform was used to regress the severity of effects on the covariate, dose. Graphs displaying s-shaped dose-response curves with 95% confidence bands were then generated. The curves are statistically derived and use all of the available toxicity data in determining the risk of adverse effects at given doses.

The proposed regression procedure should be useful in risk-based decisions that can directly use animal data. For example, the Margin of Exposure (MOE) method compares the existing exposure with the NOAEL for the critical effect. The MOE method could then be augmented by considering the estimated risk at the existing exposure and not just the MOE ratio.

The progress described above does not, however, provide a final solution to the risk problem. Some difficulties arise because of the data available for analysis. Almost all of these data are from animal studies, so the risk estimates produced by the regression are animal risk estimates that must be a manipulated further to produce human risk estimates. Thus, more research is needed to produce human risk estimates for exposures above the RfD. Also, each record in the data set represents information from an entire dose group, not from an individual animal. The interpretation of the animal risk estimate depends, then, upon the fact that the unit of input to the regression is the dose group.

Recommendations

Additional research is necessary to ensure that this categorical regression procedure is successful in estimating risk levels at specific doses. Examples of areas requiring further research are as follows:

1. Methods need to be developed that will validate the assumptions made by the model whenever the regression is performed.
2. The goodness-of-fit measures provided by the regression procedure need to be evaluated relative to their usefulness for dose-response modeling. New goodness-of-fit measures need to be developed.
3. Data should be found and analyzed that allow characterization of individual animal effects, instead of dose group effects.
4. An investigation should be made of other models that may be superior in their predictive abilities to the logistic model.
5. The enigma of the extrapolation of animal risk to human risk is thus far unsolved by this process. Ways to develop a human risk estimate need to be found.

References

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The complete report, entitled "Statistical Methods for Estimating for Exposure Above the Reference Dose," (Order No. PB 90-261 504/AS; Cost: $.8,00 subject to change) will be available only from:

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