Principles of Route-to-Route Extrapolation for Risk Assessment

Proceedings of the Workshops on Principles of Route-to-Route Extrapolation for Risk Assessment held March 19–21, 1990 in Hilton Head, South Carolina and July 10–11, 1990 in Durham, North Carolina.

Editors

Timothy R. Gerrity
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina

Carol J. Henry
ILSI Risk Science Institute
Washington, DC

Associate Editors

Linda Birnbaum
Christopher DeRosa
R. J. Dutton
Fred Miller
Lorenz Rhomberg

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SUMMARY REPORT OF THE WORKSHOPS ON PRINCIPLES OF ROUTE-TO-ROUTE EXTRAPOLATION FOR RISK ASSESSMENT

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BACKGROUND

Humans are exposed to a myriad of environmental pollutants through inhalation, ingestion, and dermal absorption. The pollutant's dose to internal target organs (the absorbed dose) is partially determined by the route of exposure. The structure, function, and metabolism of the portal of entry modulate the dose of pollutant and its metabolites that enter the circulation system for distribution to the rest of the body. In addition, the pollutant may express its toxic effect in the portal of entry itself.

Under a variety of legislation, the U.S. Environmental Protection Agency (the U.S. EPA) and other federal and state regulatory agencies are charged with protecting human health from harmful effects of environmental chemicals. For pollutants, the U.S. EPA conducts a quantitative risk assessment to determine the daily exposure dose from a particular route of exposure that is not anticipated to cause significant risk over a lifetime of exposure. Frequently, these risk assessments are conducted based on limited data. In some cases, data are not available for the route of exposure being considered, but are available for another route. For these substances, the U.S. EPA must determine whether the data can be extrapolated to the route being assessed.

At present, the U.S. EPA has no formal guidelines for route-to-route extrapolation for noncarcinogens. However, route-to-route extrapolation is done routinely by different EPA program offices, often using empirically derived factors that are not necessarily applicable to the case at hand. For example, the U.S. EPA has derived approximately 15 to 20 oral reference doses from inhalation data [1]. For these risk assessments, it is assumed (in the absence of other information) that absorption via the oral route is complete (i.e., 100%), whereas absorption via inhalation is 50% that of oral.

Currently, the U.S. EPA method for assessing the risk of carcinogens (the linearized multistage model) assumes that the same total daily body burden will give the same tumor incidence regardless of the route of exposure. Thus, the approach generally does not consider that some tumors at the site of contact (e.g., following topical application) may be site-specific, or that the dose to a target organ may be modulated by the route of exposure.

Route-to-route extrapolations are also performed by other federal and state regulatory agencies. The state of California, for example, considers it prudent risk assessment policy to assume, in the absence of data, that a substance that causes cancer when ingested will also cause cancer when inhaled, and vice versa [2]. The Department of Health and Human Services assumes 100% absorption across species,

regardless of the route of exposure, in the absence of valid evidence to the contrary [3].

For most route-to-route extrapolations, the lack of data, lack of ability to interpret data, and underutilization of existing data due to insufficient models and statistics reduce the validity of these extrapolations. At present, little is known about absorption characteristics, the potential for portal-of-entry effects, and the potential for first-pass metabolic effects for most compounds by most routes. Few studies are currently designed to test toxicity across routes. Despite this lack of data, immediate regulatory needs often necessitate route-to-route extrapolation.

Development of scientifically based principles, procedures, and data for route-to-route extrapolation would improve the validity of risk assessments, which in turn would better ensure protection of human health while avoiding overregulation and underregulation. It would also help to make the risk assessment process more efficient, an important factor considering that federal and state agencies must regulate hundreds of chemicals in the environment. Identification of research needs will help these agencies plan future research to address the problems of route-to-route extrapolation.

The workshops documented in this publication were intended to be the first step in an iterative process. The principles, conclusions, and recommendations derived from the workshops and presented in this summary report will help provide a scientific foundation for route-to-route extrapolation. Additional research on assumptions and scientific aspects of route-to-route extrapolation will require periodic revision of this foundation and any methodologies developed from it to incorporate new information.

REFERENCES

1. U.S. Environmental Protection Agency, Integrated Risk Information System (IRIS) Data Base. Accessible through the U.S. EPA E-Mail, DIALCOM E-Mail, or the Public Health Network (1990).
2. California Department of Health Services, Guidelines for Chemical Carcinogen Risk Assessment and Their Scientific Rationale. (California Health and Welfare Agency, Department of Health Services, Sacramento, CA 1985).
3. B.A. Owen, Reg. Toxicol. and Pharmacol. 11:237-252 (1990).

FACTORS GOVERNING ABSORPTION AND TARGET TISSUE DOSE

Absorption

A few basic processes govern absorption across a barrier. In the abstract, they are similar among barrier types: one must determine whether the flux is limited by delivery to the barrier (in the carrier medium), removal from the other side of the barrier, or by the rate of crossing through the barrier; one must account for competing removal processes (e.g., evaporation from skin, transit through the gut, exhalation of unabsorbed material); the existence of capacity-limited steps must be identified; and binding and partitioning in various media must be accounted for.

Factors Governing Absorption

Physico-chemical characteristics of the compound.

- Dissociation state
- Molecular size
- Molecular weight
- Partition coefficient
- pKa
- Reactivity
- Solubility
- Volatility

Exposure factors.

- Concentration
- Contact duration
- The dosing pattern
- The dosing vehicle
- The fed or fasted state of the test species
- Frequency of exposure
- Occlusion
- Release from vehicle
- Transit/residence time

Portal-of-entry factors.

- Barrier capacity as related to variability in species and individuals
- Blood flow rate
- Cell turnover
- Cell types and morphology
- Contact site
- Contact area
- Contact duration

- Diffusion to blood
- Intactness of organ
- Metabolism
- pH of the portal of entry
- Recirculation
- Specialized absorption sites
- Storage in cells

Target Tissue Dose

The actual impact of exposure by different routes cannot be predicted solely on the basis of the change in barrier function. The relationship between absorbed dose and target tissue dose can be very complex due to nonlinear systemic factors such as saturable metabolism, binding, and cofactor depletion. In addition, oral uptake presents the compound to the liver, where it is available for first-pass metabolism prior to entry into the systemic blood. This is in contrast to inhalation and dermal absorption, where the compound does not encounter the liver before entering the systemic circulation. The target tissue dose results from the convolution of these factors with the dose-rate variation induced by the barriers.

A full description of the absorption, distribution, metabolism, and elimination of the chemical is required to accurately predict the effect of changing the route of entry of the compound. The development of such a description involves the identification of systemic parameters in addition to the barrier parameters listed above.

Systemic parameters.

- Metabolism/clearance
- Tissue binding
- Tissue blood flows
- Tissue/blood partition coefficients
- Tissue volumes

The Role of PB-PK Modeling

An additional benefit of providing a physiologically based pharmacokinetic (PB-PK) description of the animal-chemical system is the ability to change the physiological and biochemical parameters in the model from those for the test species to those appropriate for humans. This approach is often preferable to sole reliance on the animal route-to-route data in human risk assessment because properties of the barriers and metabolic competency can vary greatly among species. These differences, if not treated quantitatively, can lead to highly uncertain conclusions concerning human risk based on

the animal results. Use of a model does not, of course, replace the collection of animal data. However, it can greatly improve the design and interpretation of the animal studies. Properly designed animal studies, in turn, provide the information necessary to validate the predictive value of the model.

DECISION TREE AND METHODS FOR ROUTE-TO-ROUTE EXTRAPOLATION

Decision Tree

The ability to perform quantitative route-to-route extrapolation is critically dependent upon the amount of scientific data that have been collected. Regardless of the toxic endpoint being considered, a minimum of information is required to construct plausible dosimetry by the other routes of interest. This information includes both the nature of the toxic effect and a description of the relationship between the administered dose and the ultimate biological outcome. Evaluation of the adequacy of the information available on a chemical is the first step in a decision tree used to select the most appropriate method of performing a route-to-route extrapolation on that chemical, as shown in Figure 1.

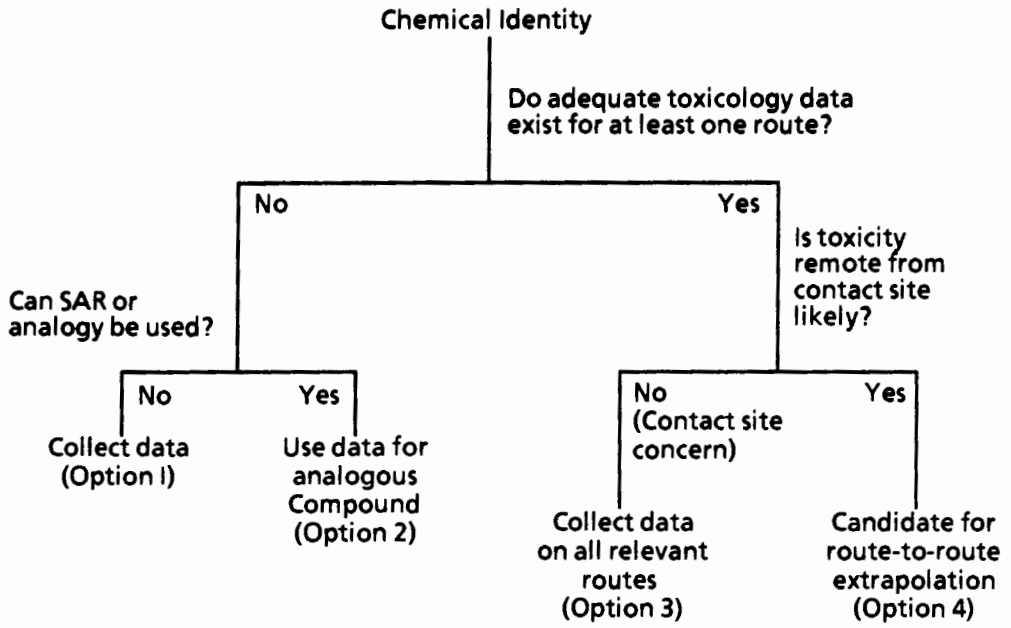

Figure 1. Decision Tree for Route-to-Route Extrapolation (see text below for a discussion of the options listed).

OPTION 1: No data/analogy available on test compound. If data on the chemical of interest are not available, it may be possible to estimate the effects of the chemical by structure-activity relationships or at least informal analogy to a related chemical for which such data do exist. If not, there is no recourse but to collect toxicity information on the chemical for at least one route of administration. Otherwise, conclusions drawn regarding either the hazard identification or quantitative risk assessment will be highly uncertain.

OPTION 2: Inadequate data available on test compound but adequate data available on similar compound. If data on a related compound are available, at least hazard identification with regard to the various routes can be performed for the test compound based on the analogous compound's toxicity.

OPTION 3: Data on compound suggest that significant risk of toxic effect is confined to the initial site of contact with tissue. If the toxicity of the chemical is dominated by a local direct effect on the tissue in the portal of entry, then a calculation of toxicity by another route of entry is not meaningful. The other routes of interest must be evaluated by direct experiment. The case study on ethyl acrylate presented by Dr. C. Frederick demonstrates the approach that can be taken for chemicals in this category.

Examples of compounds that could fall into this category are insoluble particulate materials and highly reactive chemicals. In addition, some soluble particles may belong in this category if the toxicity depends on the generation of high local concentrations of the toxic chemical by rapid dissolution of the particles. Extrapolation among routes would be highly uncertain if data suggest that a possibility of contact site toxicity exists. If the nature of the chemical suggests possible contact site effects and there exist no appropriate toxicological data for the route of interest, extrapolation should not be attempted.

On the other hand, the fact that the effect of a chemical is observed in the portal of entry does not necessarily preclude route-to-route extrapolation. The case study on cadmium presented by Dr. G. Oberdörster demonstrates the use of a pharmacokinetic model to assess the relative risk of lung effects from inhalation versus oral exposure. As pointed out by Dr. Oberdörster, however, it is possible that cadmium presented to the lung via the systemic circulation does not have the same effect observed for presentation in inhaled particles. This case study by showing a great disparity in toxicity by different routes emphasizes the point that dosimetry should be established for each relevant route of exposure before extrapolation is attempted.

OPTION 4: Data on compound suggests that toxicity is a result of delivery to a target tissue which could be remote from the site of entry. The premise for this option is that once a chemical penetrates the systemic circulation, its kinetic behavior is essentially independent of exposure route. Thus the route of entry serves only to modulate delivery to the systemic circulation. Chemicals in this category are candidates for route-to-route extrapolation. The comparison of dermal and inhalation uptake of organic vapors presented by Maj J. McDougal provides an excellent example of the power of route-to-route extrapolation modeling.

Methods for Route-to-Route Extrapolation

Use of default absorption values. Where pharmacokinetic data are inadequate or unavailable, the simplest approach for calculating the route-to-route correspondence is to use default absorption values for each exposure route appropriate to the chemical class.

One promising possibility is the evidence that there is a similar relationship across exposure routes between uptake rate and the octanol/water partition coefficient for a given class of chemicals. This simplistic approach entails an increased uncertainty compared to the use of pharmacokinetic data and PB-PK modeling. Additional factors to reflect this uncertainty should be considered in the calculation of the risk by the estimated route.

Direct measure of absorption efficiency. An improvement on the use of default values is the direct measurement of the absorption efficiency by the routes of interest. This approach still ignores potentially important factors including metabolism at the portal of entry and other first- pass and dose-rate effects.

Measure of bioavailability by internal marker. An internal measure of bioavailability provides greater certainty than an external measure. Examples of internal measures include circulating blood levels or area-under-the-curve of the parent compound or a toxic metabolite. Also, biological markers such as blood cholinesterase activity, enzyme elevation, or other clinical chemistry results, and amount of chemical bound to tissue DNA or protein could provide a measure of internal dose in specific cases.

Development of a comprehensive delivered dose description: The preferred method for performing a route-to-route extrapolation involves the development of a pharmacokinetic model of the absorption, distribution, metabolism, and elimination of the compound. Pharmacokinetic studies quantify the relationship between the external dose and the target tissue dose, incorporating

nonlinearities due to saturable metabolism, binding, depletion of critical cofactors, and such.

For example, first-pass effects in the liver after oral administration can confound the simpler methods already discussed for performing route-to-route extrapolation. In contrast, factors such as first pass effects and portal-of-entry metabolism can be effectively described by PB-PK models. The case study presented by Dr. J.Fisher on TCE illustrates the usefulness of a carefully developed PB-PK model for prediction of route-to-route differences.

Although the development of a full pharmacokinetic model can involve greater time and effort than the previous methods, it provides a considerable improvement in the reliability of the extrapolation across routes. The use of an existing model structure (template) for an analogous compound can greatly reduce the effort required for model development.

A key issue in the development of the model is the choice of the dose surrogate for the toxic effect. The closer the chosen dose surrogate is correlated with the toxic effect, the more accurate this approach will be with respect to use in quantitative risk assessment. Depending on the nature of the toxic effect, the incorporation of pharmacodynamic processes into a full biological response model may be necessary to accurately predict toxicity for different exposure scenarios. The case study on chloroform presented by Dr. R. Corley demonstrates the process of moving the dose surrogate closer to the biological effect.

CONCLUSIONS

- We lack a coherent animal and human data base for conducting route-to-route extrapolation. Development of such a data base will require a multidisciplinary approach.
- There is currently no formal methodology for route-to-route extrapolation. This is due, in part, to a lack of understanding about the function and characteristics of the three major organs of xenobiotic disposition. Development of scientifically based principles and procedures for route-to-route extrapolation would help improve the validity of risk assessments, which in turn would better ensure protection of human health while avoiding overregulation and underregulation. Ideally, these efforts would culminate in the development of an array of different protocols with variable data requirements and different decision criteria depending on the goal or risk assessment issue.

- In route-to-route extrapolation, dose-response data from one route of exposure are used to define relationships among applied (external) dose to the portal of entry, delivered dose to the target organ(s), and effects via other routes. In general, route-to-route extrapolation should not be conducted if there are recognized portal effects at the site of entry or first-pass effects (in which the barriers, as well as the liver, function as a metabolizing organ), unless there are reliable data that permit a characterization of their effect on delivered dose and/or altered function.
- Models can be valuable tools for route-to-route extrapolation. Some models currently exist, with varying degrees of complexity, accuracy, and range. Much work needs to be done to further refine and validate existing models and to develop new models. In many cases, insufficient data are currently available to develop sophisticated models for route-to-route extrapolation. Studies such as those recommended in the following section should be conducted to generate the data needed for model development.
- In principle, there is no problem with constructing models for route-to-route extrapolation. However, barrier models must consider both absorption and metabolism. If the portal of entry is affected by the agent, then a more complicated model is required. If it is not, then a simpler model of the barrier function would suffice.
- Because of the complexities of the various organ systems as portals of entry, empirical data, where available, should be used to validate models used for route-to-route extrapolation.
- The skin, the gastrointestinal tract, and the respiratory tract share a common histogenic heritage and therefore have certain common features.
- All three organs can be visualized as consisting of different anatomic regions, whose characteristics affect the potential for disposition of xenobiotics. Therefore region-specific models may be important for each route of entry.
- There may be significant differences within the human population in factors affecting absorption through the respiratory tract, gastrointestinal tract, and skin.
- The concentration of the xenobiotic at the point of entry determines local effects.
- A substance's fate is usually independent of route once it enters the systemic circulation.

- The route of exposure may have profound dose-rate effects on the target organ.

RECOMMENDATIONS

- A critical literature search study should be conducted to determine the available data on disposition by different routes for different classes of chemicals. In particular, the search should address quality of methods.
- An in-depth review should be conducted to compare the structure and function of the respiratory tract, skin, and gastrointestinal tract as portals of entry for xenobiotics.
- Research in route-to-route extrapolation should continue with focused studies on a few chemicals across several routes of administration to better understand the processes involved in disposition across barriers. Over time, as sufficient numbers of chemicals are studied, an understanding of absorption and metabolism for various chemical classes may then be developed.
- Investigators should routinely identify, measure, and validate markers of exposure that are correlated with the toxic response from the test compound.
- Concurrent pharmacokinetic studies relating exposure to any internal markers are strongly encouraged for all routes of exposure to facilitate route-to-route extrapolation.
- Given the regional heterogeneity within each of the three organ systems, the unique attributes of each of these regions should be further investigated as applies to route-to-route extrapolation.
- Research should be conducted to determine the differences and similarities between various cell types in different routes and different species, for example, macrophages in the lung versus the pleural cavity versus the peritoneal cavity.
- The contribution of the microbiological flora in route-to-route extrapolation should be evaluated.
- Models should be developed for volatilization from the skin surface, desquamation, and the effect of metabolism on bioavailability, including structure-activity relationships and the study of the absorption of hydrophobic compounds.
- Research should be conducted to determine whether any segments of the human population (e.g., people of different age, gender, or race) are particularly susceptible to xenobiotic absorption or portal-of-entry effects by the various routes.

- Research should be conducted to examine how particles and fibers deposit and absorb in the gut versus the respiratory system.
- The kinetics of gastrointestinal absorption of volatile organics and a variety of other compounds should be studied to generate provisional models of uptake for comparison with experimental data.
- Physiological parameters should be characterized for several species, especially in fat which has a major impact on the distribution and kinetics for lipophilic chemicals.
- Vehicle effects should be studied to determine their contribution to different routes of exposure.
- Rapid techniques for determining partition coefficients should be developed and validated for nonvolatiles.
- Experimental techniques should be developed and validated, using whole organs, tissue slices, and intact cells, that could be used to estimate biochemical parameters for chemical metabolism.

SUMMARY DOCUMENT WORKGROUP

Timothy Gerrity
Carol Henry
Robert Bronaugh
Lt Col Harvey Clewell
Jan Connery
Christopher DeRosa
R.J. Dutton
Clay Frederick
Larry Hall
Kim-Chi Hoang
Annie Jarabek
Francis Marzulli
Ernest McConnell
Frederick Miller
Lorenz Rhomberg