The Practical Applicability of Toxicokinetic Models in the Risk Assessment of Chemicals

Editors: J. Krüse, H.J.M. Verhaar, W.K. de Raat

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LIST OF CONTRIBUTORS

Dr. Bas J. Blaauboer
Associate Professor of Toxicology, Research Institute of Toxicology, Utrecht University, P.O. Box 80176, 3508 TD Utrecht, The Netherlands. Tel: +31 (0)30 2535330, Fax: +31 (0)30 2535077, e-mail: b.blaauboer@ritox.vet.uu.nl.

Dr. P.C. de Bragt, R. Tox.
Senior Officer of Public Health, Ministry of Health, Welfare and Sports, Inspectorate for Health Protection, P.O. Box 20350, 2500 EJ The Hague, The Netherlands. Tel: +31 (0)70 3405060, Fax: +31 (0)70 3405435.

Dr. Anette L. Bunge
Professor, Chemical Engineering and Petroleum Refining, Colorado School of Mines, Golden, CO 80401, USA. Currently at: Colorado State University, Fort Collins CO 80523, USA. Tel: +1 509-376-8462, Fax: +1 303-273-3730.

Dr. Richard A. Corley
Staff Scientist/Technical Group Leader, Chemical Dosimetry Group, Molecular Biosciences Group, Pacific Northwest National Laboratory, 902 Battelle Blvd, P.O. Box 999, MSIN P7-59, Richland, WA 99352, USA. Tel: +1 509-376-8462, Fax: +1 509-376-9064, e-mail: ra-corley@pnl.gov.

Dr. A.M. Jarabek
Research Toxicologist, National Center for Environmental Assessment, US-EPA, USA. Tel: +1 919-541-4577, Fax: +1 919-558-1213, e-mail: jarabek.Annie@epamail.epa

Dr. Pierre O. Droz, PD, CIH
Scientist, Institute for Occupational Health Sciences (IST), Lausanne University, Rue du Bugnon 19, CH-1005 Lausanne, Switzerland. Tel: +41 21-314-74, Fax: +41 21-314-7420, e-mail: pierre-olivier.Droz@inst.hospvd.ch.

Prof. Dr. V.J. Feron
Professor Emeritus, Utrecht University, Utrecht, The Netherlands. Tel: +31 (0)30-6959408, Fax: +31 (0)30 6960264, e-mail: v.jferon@freeler.nl.

Dr. Anette Kopp-Schneider
Senior Statistician,Central Unit Biostatistics, German Cancer Research Center, P.O. Box 101949, D-69009 Heidelberg, Germany. Tel: +49 6221-422-391, Fax: +49 6221-422-397, e-mail: kopp@dkfz-heidelberg.de.

Dr Jacob Krüse
OpdenKamp Registration & Notification, Koninginnegracht 23, 2514 AB The Hague, The Netherlands. Tel: +31 (0)70-426-0000, Fax: +31 (0)70-426-0001, e-mail: Krüse.j@oag.np.

Dr. John W. Nichols
Scientist, U.S. Environmental Protection Agency, National Health and Environmental Effects Laboratory, Mid-Continent, Ecology Division, 6201 Congdon Boulevard, Duluth, Minnesota, 55804, USA. Tel: +1 218-529-5160, Fax: +1 218-529-5003, e-mail: nichols.john@epa-gov.

Dr. K. de Raat
Director, OpdenKamp Registration & Notification, Koninginnegracht 23, 2514 AB The Hague, The Netherlands. Tel: +31 (0)70-426-0000, Fax: +31 (0)70-426-0001, e-mail: raatde.k@oag.nl.

Dr. Charles A. Timchalk, DABT
Staff Scientist, Molecular Biosciences Group, Chemical Dosimetry Group, Pacific Northwest Division, Batelle, Battelle Boulevard, Richland, WA., 99352, USA. Tel: +1 509-376-8462, Fax: +1 509-376-9064.
e-mail: charles.timchalk@pnl.gov.

Dr. Henk J.M. Verhaar
OpdenKamp Registration & Notification, Koninginnegracht 23, 2514 AB The Hague, The Netherlands. Tel: +31 (0)70-426-0000, Fax: +31 (0)70-426-0001, e-mail: Verhaar.h@oag.nl.

PREFACE

W.K.DE RAAT

Director OpdenKamp Registration & Notification, The Hague, The Netherlands

This symposium is concerned with a recognized problem area in especially regulatory toxicology. Effects in humans of the exposure to chemical substances are predicted from the results of toxicological studies with experimental animals. This prediction usually employs as a starting point an experimental exposure level of a certain animal species which lies just below the lowest level still causing an adverse effect in this species. The extrapolation from this so-called No Observed Adverse Effect Level (NOAEL) to a threshold level for human exposure is often solely based on the application of rather arbitrary extrapolation factors which are meant to cover all known and unknown differences between the animal in the experimental situation and man in real life. To ensure the outcome of extrapolation to be on the safe side, a worst-case strategy is followed, which simply means that large factors are chosen. Interestingly, usually no guarantee of safety can actually be given.

For a more realistic and tailor-made extrapolation, science-based factors are needed, taking into account the differences in kinetic and dynamic behaviour of a compound in different animal systems. Such factors might be derived on a case-by-case basis from:

- physicochemical properties of the substance;
- biochemical properties of the substance;
- general knowledge on the physiology determining toxicokinetics and metabolism in man and experimental animals.

To integrate this information in an adequate way, and incorporate it in predictions of safe levels, mathematical models are indispensable.

The obvious need for a more science-based extrapolation has resulted in extensive research efforts and a number of most promising toxicokinetic models. However, this has hardly resulted in a significant improvement of day-to-day risk assessment. A reason for this gap between developers of models and the risk assessors for whom they are ultimately intended might be a lack of communication. Clarity is needed on the tools wanted by the risk assessor, and information is needed on what is really possible with the models.

The organizing of this symposium was prompted by the concern about the arbitrary character of the extrapolation methods generally used and the unused possibilities of current toxicokinetic models. Experts in toxicokinetic modelling will demonstrate the possibilities and limitations of their models. It is hoped that this will trigger a discussion about the use of the models in day-to-day risk assessment.

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1 THE PRACTICAL APPLICABILITY OF TOXICOKINETIC MODELS IN THE RISK ASSESSMENT OF CHEMICALS

V.J.FERON

Professor Emeritus, Utrecht University, Utrecht, The Netherlands

1.1 Introduction

In the early days of modern toxicology, say about half a century ago, major goals of toxicity studies were the detection of the critical adverse effect of the chemical and the establishment of the dose-effect/response curve including the "No-Observed-Adverse-Effect-Level" (NOAEL). Starting from the overall NOAEL, using body weight for scaling up between experimental animals and humans, and applying uncertainty factors to compensate for intra- and interspecies differences, a "safe" dose for humans was calculated. It is sad to observe that today too often we are still doing the same thing when recommending health-based exposure limits as the basis for setting standards.

Early on toxicologists realized that knowledge about both the movement and fate of a chemical within the body (toxicokinetics) and also about the mechanism underlying the toxicity, would be of great help for the interpretation of animal toxicity data with respect to human health risk assessment. The most solid comparison is when toxicokinetic data are available in experimental animals and man, allowing direct analysis of the potential health risk in humans. In the absence of human toxicokinetic data, physiological or compartmental models may be used for extrapolation of animal data to man (Feron *et al.*, 1990).

1.2 Underlying Principles of Toxicokinetic Models

Before discussing *"The Practical Applicability of Toxicokinetic Models in the Risk Assessment of Chemicals "*, we need to understand the underlying principles of the models in both biological and mathematical terms. The physiological approach relies on the scale-up between animals and man of such parameters as tissue volume and blood flow and on their relation to body weight. Assuming that the uptake from blood to tissue (extraction ratio) is a function of the chemical and thus independent of species, it is possi-

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ble to derive (complex) models involving major organs. Alternatively and more pragmatically, the plasma toxicokinetics in various animal species may be fitted by compartmental modelling followed by scaling up empirically according to the body mass of the species examined and than to man (Renwick, 1989).

Application of such models would mean that risk assessment is based on scientific principles and understanding, implying that knowledge has been substituted for ignorance; ignorance which is often so terribly visible by the use of large uncertainty factors.

1.3 Lack of Data

Clearly, availability or lack of relevant data is one of the major factors related to the question whether or not toxicokinetic models are or can be applied in everyday risk assessment. Hazard identification including dose-effect/response curves and extrapolation of experimental data obtained in animals or humans to projected human exposure scenarios, constitutes the basis for the recommendation of so-called health-based intake levels or exposure limits. This first step in risk assessment or standard setting deals, and indeed should deal with toxicological data and health considerations only (Feron *et al.*, 1994; Feron, 1998). However, it is not exceptional that the toxicological data base, even for a widely used, high-production volume chemical, is too poor to justify the recommendation of an exposure limit. With too poor a data base, I do not mean lack of (sophisticated) toxicokinetic information but just insufficient straightforward toxicity data from repeat exposure studies such as for example a 4- or 13-week study in rats. Occasionally, some basic information about absorption, distribution , metabolism and/or elimination is available, but hardly ever to an extent and of a quality that would allow the data to be fed into a model for quantitative risk assessment. It is just the lack of information that precludes the use of any toxicokinetic model.

1.4 Use of Structure-Activity Relationships (SARs)

Toxicity is dependent on the chemical structure of a substance, its toxicokinetcs and its metabolic reaction pathways. Available metabolic pathways are usually dose dependent and, to a large extent, govern the magnitude of the toxic effect. Therefore, chemical structure, toxicokinetics, metabolic fate and dose are key elements of toxicity and play a crucial role in the safety evaluation of chemicals. Refinements of initial concepts of SARs were the result of increasing knowledge, and increased the confidence in predicting SARs. However, to my knowledge and in my experience, the use of SARs in safety

evaluation of chemicals is rather limited. Has the use of SARs been sufficiently tried? Does it not work? Is it too complicated? Are SAR experts not interested or not involved in risk assessment? One thing I know for sure is that, except for the safety evaluation of flavouring substances, the risk assessments I have been involved in hardly ever used (quantitative) SARs. Indeed SARs play an important role in the safety evaluation of flavouring ingredients, and the use of SARs has been widely accepted for this category of food chemicals. This may be due mainly to large margins of safety as a consequence of the generally low intakes and often low toxicity of flavouring substances, and also to the production of "safe" metabolites (Munro *et al.*, 1999).

1.5 Standard Tests versus Compound-Specific studies

Guidelines and detailed protocols for standard tests are common in applied toxicology. For registration purposes defined sets of tests are required. These guidelines enabled worldwide standardization and harmonization of toxicity testing which was a good thing. However, the reverse side of the medal was discouragement of the development of alternative ways to develop toxicity profiles of chemicals. Thus, although the guidelines have been of great help, and still are key elements of toxicity testing, in my view we gradually have to get rid of rigid guidelines and predetermined sets of standard tests. The conduct of whole packets of such tests should be replaced by step-by-step investigations guided by decision trees for different production and use categories of substances. The toxicology is ready to conduct such compound-specific investigations, using biochemical, cellular and tissue culture techniques, including methodologies for measuring gene expression, and last but not least, tailor-made toxicokinetic modelling. I do believe that a drawback of the prominent presence of (OECD-)guidelines for standard tests is negligence of toxicokinetic and mechanism of action studies. Of course, for some widely used chemicals of great commercial interest and with major potential health risks, complex toxicokinetic models have been and are being developed because of the need of very accurate risk estimates. An illustrative example of what can be done is the development of a very sophisticated data- and parameter-rich clonal growth model for formaldehyde by the Chemical Industry Institute of Toxicology (CIIT). The model incorporates over twenty years of research on formaldehyde, and integrates various toxicological, mechanistic and dosimetric data, and greatly reduces the uncertainty levels associated with cancer risk estimates for inhaled formaldehyde (CIIT, 1999).

1.6 Application of Toxicokinetic Data in Hazard Identification

Regulatory agencies and experts committees often shrink back to abandon familiar approaches for hazard identification and risk assessment despite conspicuous scientific shortcomings and clear disadvantages in comparison with newer more sophisticated approaches. Using new methodologies requires courage and a vulnerable disposition, and, most important, the right expertise. One (almost historical) example is the use of body weight (to the power1) versus caloric demand (metabolic rate/body weight to the power 0.75 or 0.67) for scaling up the dose in (small) experimental animals to (large) humans. Although in many cases the use of caloric demand is scientifically more justifiable, body weight (to the power 1) is just routinely still widely used as the basis for dose adjustment. Another example is the use of the benchmark dose (BMD) approach instead of the NOAEL- approach. Although the BMD approach has been shown to be useful and applicable in hazard identification, and indeed helps in getting a more complete picture of the toxicity of a chemical, among other things by dose-response modelling and derivation of critical effect doses for various endpoints, its use in standard setting is still rather limited. Is the BMD approach too complex? Although, indeed it is easier to identify the critical study and the overall NOAEL, and to extrapolate from there, the somewhat greater complexity of this much better and scientifically much sounder approach should not be an excuse not to use it.

In my view the same is true for the use of toxicokinetic models. They may be very complex, and precisely a decade ago we stated in a paper on the extrapolation of animal data to humans: "However, in view of the complexity of these models, it is anticipated that their use will remain restricted", but we also stated: "It should be emphasized that even short-term toxicokinetic data (ADME) including identification of metabolite profiles in test species would certainly make more confident interspecies extrapolation possible" (Feron *et al.*, 1990).

I think, overall, it is the combination of lack of relevant data, the existence of rigid guidelines for toxicity testing, and the reluctance of advisory committees and regulatory agencies to adopt the use of somewhat more complex techniques for hazard identification, which hampers the use of applicable toxicokinetic models in risk assessment. I am convinced that this symposium will contribute significantly to a better insight in the present state of affairs regarding the practical applicability of toxicokinetic models in risk assessment. My conviction is simply based on the presence of so many experienced experts who will discuss various aspects of toxicokinetic models and their applicability and application in risk assessment. I do hope this

symposium will stimulate the use of toxicokinetic models in hazard identification and risk assessment. I am sure we will have a very instructive and fruitful meeting, because I believe in the strength of discussion based on facts (data), expertise and experience.

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2 PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING OF THE GLYCOL ETHER, 2-BUTOXETHANOL, AND ITS APPLICATION IN HUMAN HEALTH RISK ASSESSMENTS AND EXPOSURE GUIDELINES

RICHARD A. CORLEY

Chemical Dosimetry Group, Pacific NW Nat'l Laboratory, Richland, WA, USA

Abstract: 2-Butoxyethanol (BE), is the most widely used glycol ether solvent with a variety of industrial and consumer applications. BE has, therefore, been the subject of numerous risk assessments and exposure guidelines. Exposure guidelines have been based upon findings of intravascular hemolysis in laboratory animals although it was recognized as early as the 1950's that humans were significantly less sensitive. The species-specificity in hemolysis has prompted numerous investigations into potential mechanisms of action and the relative roles for pharmacokinetics and pharmacodynamics in assessments of human health risk. While the precise mechanism remains elusive, the major metabolite of BE, butoxyacetic acid (BAA), has clearly been shown to be responsible for hemolysis. Thus, the ability to predict the concentrations of BAA in blood as a function of dose, route of exposure and species represents an important opportunity for improving the biological basis in human health risk assessments. To fulfill this need, a physiologically based pharmacokinetic (PBPK) model was developed to simulate the disposition of BE with an emphasis on the kinetics of BAA in blood of rats and humans. This PBPK model was used to determine the hemolytically relevant internal doses of BAA (both maximal blood concentrations [Cmax] and the area under the curve [AUC]) in rats following various toxicity study designs and in humans for a variety of potential oral, dermal and inhalation exposure conditions. The model was used to support a variety of exposure guidelines, including the ECETOC ILV, the ACGIH TLV, and the recent EPA IRIS RfC/RfD. In this manuscript, the circumstances and key research surrounding the development and applications of PBPK modeling to improve the biological basis for human health risk assessments for BE will be reviewed.

2.1 Introduction

Production and uses. 2-Butoxyethanol (BE; ethylene glycol n-butyl ether; EGBE; CAS No. 111-76-2; EINECS No. 203-905-0) is a member of a class of compounds commonly referred to as ethylene glycol ethers. Ethylene glycol ethers are produced by reacting ethylene oxide with various alcohols, including methanol, ethanol, propanol and butanol. As a result of their unique water and organic solubilities, ethylene glycol ethers are often used as co-solvents in both aqueous and solvent-based systems. BE is the most

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widely used of the ethylene glycol ethers with hundreds of industrial and consumer applications in paints, surface coatings, hard surface cleaners, degreasers and as a feedstock for other chemicals such as butyl glycol acetate and in phthalate and stearate plasticizers (CMA, 1997). In Europe, the total EU production of all butyl glycol ethers is ~181,000 tonnes (CEFIC, 1995). Similar production statistics have been reported for the U.S. (CMA, 1997).

Toxicity. With over 50 years of commercial use, an extensive environmental and toxicological database has been developed for BE. As early as the 1940's, BE was reported to induce hematuria/hemoglobinuria in laboratory animals (Werner *et al.*, 1943a-c). These early findings prompted several researchers to investigate the hemolytic potential of BE in various species and potential mechanisms of action. Carpenter *et al.* (1956) and Tyler (1984) have summarized many of these early research efforts. By the 1950's, it was recognized that humans were relatively resistant to the hemolytic effects of BE and that the major metabolite of BE, butoxyacetic acid (BAA) was likely to be responsible for the observed hemolysis. By the 1980's, a number of studies confirmed that BAA was responsible for hemolysis, the primary response in sensitive species following inhalation, oral or dermal exposures. Additional effects on the liver, kidney, spleen, bone marrow and to a lesser degree, the thymus have been observed but are generally considered to be secondary events related to hemolysis. The weight of evidence indicates that BE is not mutagenic, nor is it a reproductive or developmental toxicant. BE is fetotoxic only at maternally toxic (hemolytic) dose levels. The toxicity of BE has been extensively reviewed by a number of organizations in recent years (e.g. NIOSH, 1990; ECETOC, 1994; Worksafe Australia, 1996; CMA, 1997; WHO, 1998; ATSDR, 1999; EPA, 1999).

The National Toxicology Program (NTP) recently completed two-year rat and mouse inhalation bioassays with BE and have issued a draft report for review by NTP's Board of Scientific Counselors Technical Reports Review Subcommittee (NTP, 1998). In this study, groups of F344/N rats were exposed for 6 hr/d, 5 days/week at 0, 31, 62.5 and 125 ppm while B6C3F1 mice were exposed to 0, 62.5, 125 and 250 ppm BE for up to two years. Nonneoplastic lesions in both sexes of rats included Kupffer cell pigmentation in the livers and hyaline degeneration in the olfactory epithelium. Only the incidence, but not the severity, of the olfactory degeneration was exposure-related and was, therefore, considered an adaptive rather than adverse response. The Kupffer cell pigmentation resulted from hemosiderin deposition secondary to hemolysis. A NOAEL of 31 ppm and a LOAEL of 62.5 ppm was determined for noncancer effects.

In mice, nonneoplastic lesions included forestomach ulcers and epithelial hyperplasia, hematopoietic cell proliferation and hemosiderin pigmentation in the spleen, Kupffer cell pigmentation in the livers, hyaline degeneration of the olfactory epithelium (females only) and bone marrow hyperplasia (males