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Human risk assessment of dermal and inhalation exposures to chemicals assessed by route-to-route extrapolation: The necessity of kinetic data

Liesbeth Geraets *, Jos G.M. Bessems [1], Marco J. Zeilmaker, Peter M.J. Bos

National Institute for Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, The Netherlands

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ABSTRACT

In toxicity testing the oral route is in general the first choice. Often, appropriate inhalation and dermal toxicity data are absent. Risk assessment for these latter routes usually has to rely on route-to-route extrapolation starting from oral toxicity data. Although it is generally recognized that the uncertainties involved are (too) large, route-to-route extrapolation is applied in many cases because of a strong need of an assessment of risks linked to a given exposure scenario. For an adequate route-to-route extrapolation the availability of at least some basic toxicokinetic data is a pre-requisite. These toxicokinetic data include all phases of kinetics, from absorption (both absorbed fraction and absorption rate for both the starting route and route of interest) via distribution and biotransformation to excretion. However, in practice only differences in absorption between the different routes are accounted for.

The present paper demonstrates the necessity of route-specific absorption data by showing the impact of its absence on the uncertainty of the human health risk assessment using route-to-route extrapolation. Quantification of the absorption (by *in vivo*, *in vitro* or *in silico* methods), particularly for the starting route, is considered essential.

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1. Introduction

Dermal and inhalation exposures are very common in occupational and consumer exposure scenarios. Human health risks from dermal and inhalation exposures are preferably assessed by using route-specific toxicity data. However, in toxicity testing the oral route is in general first choice and often appropriate inhalation and dermal toxicity data are absent. As a consequence, risk assessment for these routes has to rely on route-to-route extrapolation using oral toxicity data. Route-to-route extrapolation can be defined as the prediction of an equivalent dose and dosing regimen for the route of interest that produces the same response (both in a quantitative and a qualitative sense) as observed for a given dose and dosing regimen by another route (Pepelko and Withey, 1985).

Although it is generally recognized that the uncertainties involved are (too) large (ECHA, 2012; IGHRC, 2006), route-to-route extrapolation is applied in many cases because of a strong need of an assessment of risks in a given exposure scenario. This need is felt within various human risk assessment frameworks in which occupational and cosmetic exposure scenarios are considered by EU bodies such as the EU Scientific Committee on Consumer Safety (SCCS) and the EU Scientific Committee on Occupational Exposure Limits (SCOEL) (SCCS, 2012c; SCOEL, 2013). Within the cosmetics framework, SCCS evaluates the safety of cosmetic ingredients and uses a Margin of Safety (MoS) approach to compare a human systemic exposure to a PoD (point of departure) being a NOAEL (no-observed-adverse-effect-level) or a BMDL (lower 95% confidence limit of the benchmark dose) for the most relevant toxicological endpoint in the key animal study (SCCS, 2012c). The majority of dossiers evaluated by SCCS include no route-specific toxicity studies for dermal exposure scenarios and, therefore, for these scenarios usually oral toxicity studies are used to set a PoD for risk assessment which subsequently includes route-to-route extrapolation. Route-to-route extrapolation is also applied in the derivation of Human Limit Values (HLVs) as for example done by SCOEL. SCOEL evaluates work-related inhalation exposure to chemicals in order to present substance-specific recommendations for occupational exposure limits (OELs) (SCOEL, 2013). Route-to-

Abbreviations: ADME, absorption, distribution, metabolism and excretion; A(O)EL, Acceptable (Operator) Exposure Level; BMDL, lower 95% confidence limit of the benchmark dose; HLV, Human Limit Value; MoS, Margin of Safety; NOAEL, no-observed-adverse-effect-level; OEL, occupational exposure limit; PoD, point of departure.

* Corresponding author.
E-mail address: Liesbeth.Geraets@RIVM.nl (L. Geraets).
[1] Current address: Systems Toxicology Unit, Institute for Health & Consumer Protection, European Commission Joint Research Centre, Via E. Fermi 2749, I-21027 Ispra, Italy.

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route extrapolation is also applied within the risk assessment frameworks of plant protection products and biocides (DG SANCO, 2006; ECHA, 2009). Acceptable Operator Exposure Levels (AOELs) are derived by the EU Member States and peer-reviewed by EFSA in order to evaluate exposure (dermal and inhalation) to plant protection products for the professionals (operator and bystander) (DG SANCO, 2006). Acceptable Exposure Levels (AELs) are derived as health-based reference values for exposure to biocides for the human population as a whole including sensitive sub-populations (ECHA, 2009, 2013). The most often applied route-to-route extrapolation includes the oral-to-dermal and oral-to-inhalation extrapolation, though the principles apply to other route-to-route extrapolations as well.

As mentioned, route-to-route extrapolation is, in absence of route-specific data, a highly uncertain procedure and only accounts for systemic effects as, for instance, acknowledged by the European Chemicals Agency (ECHA) (ECHA, 2012). The possibility of local effects for the route of interest is not and cannot be considered by route-to-route extrapolation. Many factors play a role in the processes that determine the final target tissue dose and many of these are route-specific. It has been acknowledged that for an adequate route-to-route extrapolation the availability of at least some basic toxicokinetic data is desirable (IGHRC, 2006). These toxicokinetic data include all phases of kinetics, from absorption (expressed as absorbed fraction during a required time-frame or absorption rate for both the starting route and route of interest) via distribution and biotransformation to excretion.

Q4 Previously, Pepelko (1985) as well as Rennen et al. (2004) described various criteria to be met before performing a reliable route-to-route extrapolation (Pepelko and Withey, 1985; Rennen et al., 2004):

(1) the available toxicity data are considered adequate and reliable;
(2) the critical effect(s) for the routes of exposure under consideration are systemic, and the absorption and expression of toxicity are not influenced by possible local effects;
(3) the considered toxic effect is independent of the route of exposure;
(4) the absorption efficiency is the same between routes or the difference is known and can be quantified;
(5) the half-life of the chemical is long;
(6) hepatic first pass effects are minimal;
(7) no significant chemical transformation by intestinal microflora or pulmonary macrophages takes place;
(8) the chemical is relatively soluble in body fluids.

In practice, many of these criteria are often not met. In the EU, for industrial chemicals that are regulated by the REACh legislation it is acknowledged in the Guidance published by ECHA that in risk assessment corrections should be made for differences in kinetics. Notably, it also states that, in general, it is difficult to quantify route-specific differences in metabolism, excretion and distribution (ECHA, 2012). Hence, in practice only differences in absorption between the different routes (*i.e.* differences in absorbed fraction expressed as a percentage) can be accounted for. ECHA notes that route-to-route extrapolation is associated with a high degree of uncertainty and should be conducted with caution relying on expert judgment (ECHA, 2012).

The present paper illustrates the importance of kinetic data in the reduction of uncertainties for human health risk assessment introduced by route-to-route extrapolation. As indicated before, various ADME (absorption, distribution, metabolism and excretion) parameters are considered important for human risk assessment (Bessems and Geraets, 2013). This paper will focus on the species- and route-specific parameter of absorption fraction (of both starting route as well as route of interest). Factors affecting this absorption fraction will however not be discussed, as this is considered beyond the scope of this manuscript. In the discussion of the present paper, current methods for quantifying absorption will be considered. Further, several existing guidances for route-to-route extrapolation with respect to inclusion of information on route-specific absorption fractions will be presented and discussed.

2. Consequences of applying route-to-route extrapolation without kinetic data

If information is available that points toward significant kinetic differences (qualitative and/or quantitative) between routes, route-to-route extrapolation should not be applied. However, in the daily practice of risk assessment fulfilling all the criteria mentioned by Pepelko (1985) and Rennen et al. (2004) is often not feasible. Route-to-route extrapolation is nevertheless commonly applied as a necessary and quite straightforward two-step procedure with only a correction for differences in absorption between routes (Fig. 1): (1) conversion of an external oral dose (i.e. NOAEL or BMDL) to an internal systemic dose by correcting for incomplete oral absorption; and (2) transformation of the internal animal dose to an external dose metric for the human exposure route of interest (dermal or inhalation) by taking into account the amount of incomplete dermal or inhalation absorption (de Raat et al., 1997).

2.1. Assessment factors

Risk assessments starting from animal experiments in general include application of assessment factors for interspecies differences (animal to human) and human intraspecies variability and this is not different in route-to-route extrapolation. These factors include both a subfactor for kinetics and for dynamics (Fig. 2; (WHO, 2005)) and are, for pragmatic reasons, generally applied to external exposure. If chemical-specific information is available, default values for these factors can be adapted (WHO, 2005). Such a refinement reduces the uncertainties involved in extrapolation. For instance, when applying route-to-route extrapolation, information on kinetics might be used to adapt the subfactor of 4 for kinetics of the interspecies assessment factor.

In route-to-route extrapolation two options for the application of these assessment factors in a risk assessment approach are possible, i.e. application on the external dose or on the internal dose. Fig. 3 shows the different steps in the two options (options A and B) that can be distinguished in oral-to-inhalation extrapolation, and at which specific step extrapolation factors are applied. In option A, the assessment factors are applied on the external dose metric in the final extrapolation step. Here, conversion of an internal dose (in mg/kg bw/d) to an external inhalation concentration (in mg/m^3) is based on the respiratory minute volume and body weight of the animal. This option is brought forward by ECHA as their preferred pathway (ECHA, 2012), with a slight modification (option A-I). In addition to the assessment factors, ECHA applies a correction for differences in absorption between humans and animals for the route of interest in this final step. In option B (Fig. 3) assessment factors are applied on the internal dose. First, the oral animal dose is converted to an internal dose using animal oral absorption data. Next, assessment factors are applied to convert this internal animal dose to an internal human dose. In the final step, the internal human dose is translated to an external concentration (in mg/m^3), using a human estimate for absorption and human data on respiratory volume and body weight. Option B is, although with slight differences (Fig. 3, option B-I), for instance applied within the risk assessment frameworks of cosmetics and pesticides (DG SANCO, 2006; SCCS, 2012c). The oral animal dose

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