Available online at www.sciencedirect.com
SCIENCE DIRECT®
Regulatory Toxicology and Pharmacology 39 (2004) 5–11
Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

Oral-to-inhalation route extrapolation in occupational health risk assessment: a critical assessment

Monique A.J. Rennen,* Tialda Bouwman, Annette Wilschut, Jos G.M. Bessems, and Cees De Heer

Department of Toxicological Risk Assessment, TNO Chemistry, P.O. Box 360, 3700 AJ Zeist, The Netherlands

Received 3 April 2003

Abstract

Due to a lack of route-specific toxicity data, the health risks resulting from occupational exposure are frequently assessed by route-to-route (RtR) extrapolation based on oral toxicity data. Insight into the conditions for and the uncertainties connected with the application of RtR extrapolation has not been clearly described in a systematic manner. In our opinion, for a reliable occupational health risk assessment, it is necessary to have insight into the accuracy of the routinely applied RtR extrapolation and, if possible, to give a (semi-)quantitative estimate of the possible error introduced. Therefore, experimentally established no-observed-adverse-effect-levels for inhalation studies were compared to no-adverse-effect-levels predicted from oral toxicity studies by RtR extrapolation. From our database analysis it can be concluded that the widely used RtR extrapolation methodology based on correction for differences in (estimates of) absorption is not generally reliable and certainly not valid for substances inducing local effects. More experimental data are required (from unpublished data or new experiments) to get insight into the reliability of RtR extrapolation and the possibility to derive an assessment factor to account for the uncertainties. Moreover, validated screening methods to predict/exclude the occurrence of local effects after repeated exposure are warranted. Especially, in cases where chemical exposure by inhalation or skin contact cannot be excluded route-specific toxicity studies should be considered to prevent from inadequate estimates of human health risks.
© 2003 Elsevier Inc. All rights reserved.

Keywords: Route extrapolation; Inhalation; Respiratory; Oral; Risk assessment; Local effects

1. Introduction

In the European Union, a risk assessment on human health effects is required on e.g., new notified substances (EEC, 1992), priority existing substances (EEC, 1993), pesticides (EEC, 1991), and biocidal active substances (EC, 1998). In human health risk assessment an attempt is made to identify the hazards of the substance and to relate these to the anticipated exposure. For those substances for which a threshold for toxicity is assumed to exist, a no-observed-adverse-effect-level (NOAEL) has to be derived or, if this is not possible, a lowest-observed-adverse-effect-level (LOAEL). The NOAEL is the highest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure (WHO, 1994). Subsequently, the risk is characterized by comparing estimated (or measured) concentrations in air, on skin or total daily intakes to the results of the hazard assessment. The analysis is made separately for each population potentially exposed, i.e., consumers, workers, and human exposed through the environment.

This paper focuses on risk assessment for workers. As workers are mainly exposed by inhalation and skin contact, NOAELs derived from dermal or inhalation toxicity studies are preferred as basis for the risk assessment. However, route-specific toxicity data are not a standard data requirement for the admission of pesticides and biocidal active substances, nor for notification of new substances and the evaluation of existing substances and are therefore often not available. Due to this

* Corresponding author. Fax: +31-30-694-4926.
E-mail address: rennen@chemie.tno.nl (M.A.J. Rennen).

0273-2300/$ - see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/j.yrtph.2003.09.003

frequent lack of route-specific data, the no adverse effect level (NAEL) for dermal or inhalation exposure is frequently established by route-to-route (RtR) extrapolation based on an oral NOAEL.

RtR extrapolation is defined as the prediction of an equivalent dose and dosing regimen that produces the same toxic endpoint or response as that obtained for a given dose and dosing regimen by another route (Pepelko and Withey, 1985). The general principle of RtR extrapolation is an easy and straightforward two-step procedure: step (1) conversion of the external oral NOAEL to an internal systemic dose by correcting for the amount of the compound which did not enter the body during experimental exposure as the result of incomplete oral absorption; and step (2) transformation of the internal dose to an external dose for the exposure route of interest (skin or inhalation) by taking into account the amount of incomplete dermal or inhalation absorption (De Raat et al., 1997).

Insight into the conditions for and the uncertainties connected with the application of RtR extrapolation has not been clearly described in a systematic manner. However, it is generally accepted that the following three conditions must be met for reliable application of RtR extrapolation to assess the health risks of dermal or inhalation exposure (Dethloff, 1993; Gerrity and Henry, 1990; Pepelko, 1987; Sharrat, 1988): (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. Other factors considered by Pepelko (1987) and Sharrat (1988) for a reliable RtR extrapolation are: (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; and (8) the chemical is relatively soluble in body fluids.

Although these criteria might be generally recognized, they are often not met. Yet, RtR extrapolation is widely used, often without an appropriate consideration of the inherent uncertainties. Moreover, it is not customary to correct for the uncertainties introduced due to RtR extrapolation, e.g., by means of an additional uncertainty factor. In our opinion, for a reliable occupational health risk assessment it is necessary to have insight into the accuracy of the routinely applied RtR extrapolation and, if possible, to give a (semi-)quantitative estimate of the possible error introduced. Therefore, the comparability of experimentally established NOAELs versus NAELs predicted from oral toxicity studies by RtR extrapolation was evaluated by means of a database analysis and described in this paper.

2. Methods and data analyses

2.1. Data collection

In order to derive pairs of NOAELs for oral and inhalation or dermal exposure, a toxicological database was generated using the Microsoft Corporation ACCESS 7.0 software program for WINDOWS 95 NL. The following data sources were consulted: (a) Pesticide dossiers filed in the archives of the TNO Occupational Toxicology Advisory centre (including monographs drawn up in the framework of the Council Directive 91/414/EEC (EEC, 1991)) from the period 1988 to September 1997; (b) Dossiers prepared under Council Regulation 793/93 (EEC, 1993) on Existing Chemicals until October 1997; (c) IPCS Environmental Health Criteria documents up to and including No. 186 (1976–September 1997); and (d) Reports from the Joint Meeting of the FAO Panel of Experts on pesticides in Food and the Environment and the WHO Expert Group on pesticide Residues (JMPR). To extend the database with substances for which no dermal and/or respiratory repeated dose toxicity data were available but for which well documented oral studies were available in the consulted dossiers, public literature was screened for dermal and respiratory repeated dose toxicity data on these substances, using MEDLINE and TOXLINE up to and including mid-1996.

In total, 215 test substances with a wide variety of chemical structures and physico-chemical characteristics were included in the database. For each study, the following information was filed (if applicable): test species and strain, exposure details (dose levels, vehicle, study duration, and exposure in days/week and h/day), NOAEL and LOAEL for systemic toxicity, critical systemic effect, NOAEL and LOAEL for local effects, critical local effect, and/or compliance with OECD guidelines. A lot of data originate from confidential reports therefore only limited details on the test substances can be provided in this manuscript.

2.2. Data selection

In view of the limited number of dermal repeated dose studies available, only oral and inhalation NOAELs were selected for further analysis. For a reliable comparison of experimentally established inhalation NOAELs and predicted NAELs (based on oral studies), the pairs of toxicological studies should be 'similar' in all relevant aspects (such as exposure duration, exposure levels, species, endpoints studied, etc.) except for the route of exposure. The number of oral and inhalation studies that matched in this way was small. Therefore, the following criteria were less stringently applied:

- *Exposure duration*. The studies were categorized in three groups with an exposure duration range of 3–6, 10–26, and 50–104 weeks, respectively. No

adjustment was made for their specific daily or weekly exposure.

- *Endpoints studied*. The lowest NOAEL (i.e., the NOAEL for the most sensitive effect) determined in the reported study was used (also when the NOAEL in the oral and the inhalation study appeared to be based on different critical effects). NOAELs for both systemic and local effects were used. If no NOAEL was available, the lowest observed adverse effect level (LOAEL) was divided by an arbitrary factor 3 in order to derive a NAEL. This value is about the value proposed in several publications (e.g., Dourson et al. (1996) and Alexeeff et al. (2002)). The NOAEL values derived from "limit tests" (test at one dose level) were included (although these are limits; the actual NOAEL may be (much) higher).
- *Similar test species*. Studies with different test species were used in one pair. Interspecies extrapolation was used which was based on caloric demands or metabolic body size, which is proportional to the 0.75 power of the body weight (ECETOC, 1995; Griem et al., 2002; Hakkert, 2001). Interspecies extrapolation was performed using the adjustment factors presented in Table 1.

Since the availability of substance-specific absorption data was limited, default values for oral and inhalation absorption were used. The different assumptions made were:

(a) Oral absorption is assumed to be equal to inhalation absorption (i.e., an absorption ratio of 1).
(b) One hundred percent oral and 75% inhalation absorption (i.e., an absorption ratio of 0.75): An inhalation absorption of 75% is taken as lower limit value as given in the Technical Guidance Document (TGD, 2003);
(c) Fifty percent oral and 100% inhalation absorption (i.e., an absorption ratio of 2): an inhalation absorption of 100% is taken as upper limit value as given in the Technical Guidance Document (TGD, 2003). Fifty percent oral and 100% inhalation absorption is considered a 'worst-case' default approach.

Table 1
Adjustment factors for interspecies extrapolation based on caloric demands

Species 1	Species 2	Adjustment factor for interspecies extrapolation	
		Species $1 \rightarrow 2$	Species $2 \rightarrow 1$
Dog (10 kg)	Rat (0.3 kg)	0.4	n.a.
Dog (10 kg)	Rabbit (2.5 kg)	0.7	n.a.
Monkey (3 kg)	Rat (0.3 kg)	n.a.	1.7
Rat (0.3 kg)	Mouse (0.03 kg)	0.6	1.8
Rabbit (2.5 kg)	Rat (0.3 kg)	n.a.	1.7
Rabbit (2.5 kg)	Mouse (0.03 kg)	n.a.	3

n.a., not applicable.

2.3. Data analysis

The experimentally obtained oral NOAELs were extrapolated to predicted inhalation NAELs using the different absorption assumptions for oral to inhalation exposure. The data expressed in mg/m^3 were converted into mg/kg bw/day by correcting for inhalation volume and body weight. The values used are listed in Table 2.

The predicted NAELs were compared with inhalation NOAELs obtained in the experimental studies to evaluate the accuracy of RtR extrapolation. A NAEL/NOAEL of >1 implies an underestimation of the level of toxicity, whereas a NAEL/NOAEL of <1 implies an overestimation of the level of toxicity (indicating a 'safe' extrapolation). The overall distribution of NAEL/NOAEL over >1 and $\leqslant 1$ was investigated to get insight in the frequency of the over- or underestimation of the risk. Besides, the effect of loosening selection criteria (that were abandoned to extend the data selection) on the distribution of NAEL/NOAELs was studied after re-introducing them.

3. Results

Of a total of 215 substances, the data selection resulted in pairs of oral and inhalation toxicity studies for 28 test substances. In 15 of the 28 cases the selection was based on the same critical effect. In 8 cases local effects were taken into account as well. In 10 cases interspecies extrapolation had to be applied, 11 ratios were based on an oral and/or inhalation LOAEL, 1 oral NOAEL and 3 inhalation NOAELs were based on the highest dose level tested, and in 3 oral and 7 inhalation studies selected only one dose level was tested.

The distribution and the range of the calculated NAEL/NOAEL ratios for inhalation toxicity using the three different absorption scenario's are presented in Table 3. By rough generalization it can be seen that for all three assumptions on absorption correction the number of NAEL/NOAEL ratios well below 1 is about equal to the number of NAEL/NOAEL ratios well over 1. In other words oral-to-inhalation extrapolation resulted in about 50% of the cases in an underestimation

Table 2
Overview of body weight and inhalation volume values used in conversion of inhalation repeated dose toxicity data (Paulussen et al., 1998)

Species	Body weight (kg)	Inhalation volume (x liter/min)
Mouse	0.03	0.045
Rat	0.3	0.24
Rabbit	2.5	0.3
Monkey	3	0.84
Human	70	20.8

Table 3
Range and distribution of NAEL/NOAEL over >1 and ⩽1

Absorption assumption	NAEL/NOAEL *N* absolute (relative)		Range in NAEL/NOAEL (min.–max.)
	⩽1	>1	
100% oral and 100% inhalation	12 (43%)	16 (57%)	0.03–326
100% oral and 75% inhalation	11 (39%)	17 (61%)	0.04–434
50% oral and 100% inhalation	15 (54%)	13 (46%)	0.02–163

NAEL/NOAEL ratio ⩽1, overestimation of the level of toxicity ('safe'); NAEL/NOAEL ratio >1, underestimation of the level of toxicity ('unsafe').

Table 4
The distribution of NAEL/NOAEL after the introduction of an extra criterion (assuming equal absorption)

Criterion	*N*	NAEL/NOAEL *N* absolute (relative)	
		⩽1	>1
None	28	12 (43%)	16 (57%)
Same critical effect	15	6 (40%)	9 (60%)
Same test species	18	5 (28%)	13 (72%)
Only systemic effects	20	11 (55%)	9 (45%)
NOAELs for both routes	17	8 (47%)	9 (53%)
Repeated-dose studies with identification of LOAEL and NOAEL	14	6 (43%)	8 (57%)

NAEL/NOAEL ratio ⩽1, overestimation of the level of toxicity ('safe'); NAEL/NOAEL ratio >1, underestimation of the level of toxicity ('unsafe').

of the level of toxicity (ratio >1) and in about 50% in an overestimation (ratio <1). The range of calculated NAEL/NOAELs ratios varied widely, e.g., 0.03–326 assuming equal absorption.

Examples of compounds having a NAEL/NOAEL ratio well below 1, were chloroform (NAEL/NOAEL = 0.04), 1,1,1-trichloroethylene (NAEL/NOAEL = 0.04), amitrole (NAEL/NOAEL = 0.08), and aldrin (NAEL/NOAEL = 0.08). Compounds having a NAEL/NOAEL ratio well over 1 included benzene (NAEL/NOAEL = 163–326), hexachlorocyclopentadiene (HCCP) (NAEL/NOAEL = 77), *o*-cresol (NAEL/NOAEL = 58), dichlorvos (NAEL/NOAEL = 56), and carbaryl (NAEL/NOAEL = 20). All NAEL/NOAEL ratios presented here are under the assumption that the absorption efficiency is equal for both routes.

The effect of the re-introduction of one of the criteria (that was abandoned to extend the data selection) on the number of matching studies and on the distribution of NAEL/NOAEL ratios is presented in Table 4. The results are only presented for NAEL/NOAEL ratios assuming no differences in oral and inhalation absorption. Applying none of the selection criteria results in 28 NAEL/NOAEL ratios and 57% of the ratios above 1. For each selection criterion applied again, the number of hits (*n*) decreased with 8 or more. For example applying the criteria 'same test species' resulted in 18 NAEL/NOAEL ratios (60% >1). No indication was found that the distribution of NAEL/NOAEL ratios significantly changed per criterion except for the criterion 'only systemic effects.' An indication was found that by the inclusion of substances with an overall oral or inhalation NOAEL based on local effects, the ratio NAEL/NOAEL shifted more towards >1 ('unsafe'). Applying this criteria resulted in 20 ratios of which 55% were ⩽1 and 45% were >1.

4. Discussion

The present paper evaluates the accuracy of RtR extrapolation in risk assessment as it is currently applied for the prediction of inhalation toxicity based on oral data and correction for differences in absorption. The objective was to get a semi-quantitative impression of the uncertainty introduced by oral-to-inhalation RtR extrapolation. The accuracy of oral-to-dermal RtR extrapolation could not be evaluated due to a lack of data.

From the data analysis it was found that the ratio between the oral (starting route) and the inhalation (extrapolation route) N(O)AEL could not be explained by an extrapolation factor solely based on differences in absorption. In at least 45% of all cases the NAEL/NOAEL ratio appeared higher than 1, i.e., a substance was predicted to be 'less toxic' based on RtR extrapolation compared to the actual observations in repeated-dose inhalation toxicity studies. The overall results of the present study were only slightly influenced by changing the assumptions on route-specific differences in absorption, indicating that other (unknown) factors are important in RtR extrapolation and/or that the reliability of the estimates of absorption used in this study was poor.

That other factors might play a role in route-specific toxicity was already suggested by several authors and can be illustrated by a more detailed evaluation of the toxicity data used in the present analysis. For certain compounds it appeared that differences in metabolism after oral and inhalation exposure might explain the observed route specific difference. For example, after oral administration, hexachlorocyclopentadiene (HCCP) is extensively degraded to polar metabolites in the faecal

material and gut content and the majority of the orally consumed HCCP is not absorbed (WHO, 1991). This first pass metabolism will not occur after inhalatory exposure. Furthermore, both dichlorvos (WHO, 1989) and *o*-cresol (WHO, 1995) are extensively metabolized in the liver after oral administration. After inhalation exposure, this metabolism does not occur at the port of entry. For these substances, the risk after inhalation exposure would be assessed inadequately when it is based on oral-to-inhalation extrapolation.

From the results of a subacute toxicity study with 1,4-dichlorobenzene designed to evaluate the accuracy of RtR extrapolation (Appel et al., 2003), it was also concluded that inhalatory toxicity cannot reliably be predicted from oral toxicity data, even when a good estimate of the absorption of the test substance (i.e., the internal dose) is available. In this study, the overall NOAELs for subacute oral and inhalatory exposure were 37.5 and 58 mg/kg bw/day, respectively. These NOAELs are both external doses. If calculated bioavailability values (based on AUC's) are used, internal NOAELs after oral and inhalatory administration can be estimated at about 34 and 17 mg/kg bw/day, respectively. This indicates that 1,4-dichlorobenzene is about twice as toxic after inhalatory than after oral exposure. However, these overall NOAELs are based on different critical effects. Presently, when the NOAELs for the *same* effects are considered for both dose routes, the prediction of toxicity seems poor. The overall internal oral NOAEL of 34 mg/kg bw/day is based on increased plasma cholesterol and liver pathology. The internal inhalatory NOAEL for both these parameters is 138 mg/kg bw/day, indicating that 1,4-dichlorobenzene is about four times *less* toxic to the liver after inhalatory than after oral exposure. The overall internal inhalatory NOAEL of 17 mg/kg bw/day is based on increased urinary protein (as an indication of nephrotoxicity). The internal oral NOAEL for this parameter is 540 mg/kg bw/day (based on the reversed effect: decreased urinary protein levels), indicating that 1,4-dichlorobenzene is about 32 times *more* toxic to the kidney after inhalatory than after oral exposure. This study shows that the NOAELs for similar changes in end points after inhalatory exposure are either higher or lower than after oral exposure and that these differences are not even consistent for the external and internal doses. The factor of difference between internal NOAELs among both dose routes ranges from 1 to 4, with a peak to 32, for urinary protein levels (the critical effect parameter in the inhalation study). Appel et al. (2003) concluded that, in general, these results justify the conclusion that inhalation toxicity cannot reliably be predicted from oral toxicity data, even when a good estimate of the absorption of the test substance (i.e., the internal dose) is available.

Thus, the validity of the extrapolation methodology based on only correction for differences in (estimates of) absorption could not be demonstrated in the present study. Relatively large uncertainty factors appear to be necessary to derive a NAEL equal to or lower than the actual NOAEL derived from repeated-dose toxicity studies. The NAEL/NOAEL distribution in the data analysis ranged from 0.03 up to 326 (assuming equal absorption). However, an obvious complicating factor in the present analysis was the small number of 'similar' oral and inhalation toxicity studies that were retrieved from our database. At least 8 of the 28 N(O)AEL pairs was extracted abandoning a number of important criteria (see Table 4). Another confounding factor is the lack of information on substance specific absorption values, which made it necessary to introduce default assumptions for differences in absorption. An even more complicating and unavoidable factor, however, is the inherent uncertainty of NOAELs. The NOAEL for a large part depends on the chosen dose levels and the spacing between the doses in the experimental studies (Gaylor, 1992; TGD, 2003). Due to these confounding factors and shortcomings, it is not considered valid to give a (semi-)quantitative estimate of the remaining uncertainty that is introduced when inhalation toxicity is predicted from an oral toxicity study based on this data analysis.

A large database would be required to create the situation that the shortcomings will disappear due to averaging. As only a limited number of data on toxicity after repeated dermal and inhalation exposure were found after an extensive literature search, it is doubtful whether such experimental data indeed do exist. Insight in the reliability of RtR extrapolation methodologies may then only be obtained by the generation of more experimental data.

Although, based on the considerations described above, no overall conclusion can be drawn on the validity of the routinely applied RtR extrapolation, one clear general conclusion can be drawn: 'RtR extrapolation is not valid for substances inducing local effects.' Local effects may differ for routes of exposure and influence the systemic dose. This issue was already addressed by several authors (Dethloff, 1993; Gerrity and Henry, 1990; Pepelko, 1987; Sharrat, 1988; TGD, 2003). A further scientific basis is given by the results derived in this study. A shift towards a more 'safe' extrapolation was observed when NOAELs based on local effects were excluded from the analysis. Besides, the same conclusion was drawn from recent experimental studies (Arts et al., 2003). They performed two similar subacute toxicity studies (one oral and one inhalation) with furfural to evaluate the validity of RtR extrapolation. The NOAELs for systemic effects were comparable, i.e., 96 mg/kg bw for oral toxicity and 92 mg/kg bw (corresponding to 320 mg/m^3 (6 h/day) or 640 mg/m^3 (3 h/day)) for inhalation toxicity assuming 100% absorption for both routes. However, the NOAEL for local inhalatory toxicity of

furfural, that is nasal epithelial toxicity, was below 6 mg/kg bw (corresponding to 20 mg/m^3 (6 h/day), lowest concentration tested), while no local effects were observed after oral administration up to 96 mg/kg bw. As such, furfural appears to be at least 16 times more toxic by inhalation than by oral gavage based on induction of local effects.

A comparable observation was made in a subacute toxicity study designed to compare the toxic effects of oral treatment with captan to the toxic effects of inhalation exposure to captan (Muijser et al., 2003). The results of the oral 28-day toxicity study indicated that toxic effects were limited. The lowest dose (4 mg/kg body weight) was a no-observed-effect-level (NOEL) and the mid-dose (25 mg/kg body weight) was possibly an NOAEL dependent on whether the dose-related increase in inorganic phosphate in female animals of the mid-dose group is regarded an adverse effect or not. At the levels used, inhalatory exposure did not induce any signs of systemic toxicity. This was to be expected in a case where RtR extrapolation would be valid, because the highest concentration level used, 12.5 mg/m^3, is equivalent with a daily oral dose of 3.6 mg/kg body weight, assuming 100% systemic absorption for both routes of exposure. In contrast, treatment-related histopathological changes were observed in the respiratory tract of mid- and high-concentration animals (2.5 and 12.5 mg/m^3, respectively). The low concentration (0.5 mg/m^3) was, therefore, considered the NOEL. The changes were most severe in the nasal tissues. If 100% systemic absorption is assumed for both oral and inhalatory exposure, the NOEL for inhalatory exposure is considered to be almost 30 times lower than the NOEL for oral treatment and almost 180 times lower than the possible NOAEL for oral treatment. Hence, these results indicate that the local effects of captan on the respiratory tract and in particular on the epithelial tissues of the nose occur at a much lower level than any systemic toxicity. Therefore, the results of this study add further support to the conclusion that it is not in general possible to predict the toxicity of inhalatory exposure from oral toxicity studies in case a substance induces local effects.

Using the induction of local effects as criterion to decide on the validity of RtR extrapolation in a given risk assessment requires well founded and internationally recognized test methods to predict local effects after repeated exposure. Currently, there are no internationally recognized screening methods in animals to predict the ability of chemicals to cause local effects of the respiratory tract (Bos et al., 2002; TGD, 2003). The only studies available appear to be acute irritation tests. It is known that substances inducing skin and/or eye irritation frequently induce local effects after repeated inhalation exposure. However, based on results of a database survey, it appeared that the positive predictive value of skin and eye irritation studies was only 65% for the risk of local effects after repeated dose administration. Importantly, the absence of any indication of local effects in any type of study does not exclude the occurrence of local effects upon repeated dermal or inhalation exposure (i.e., there was no negative prediction possible) (Rennen et al., 2002). Thus, the results of an (acute) irritation study give no decisive answer whether local effects after repeated exposure will occur. This indicates that, to investigate the potential to induce local effects of a compound, there are no alternatives than a route-specific repeated dose toxicity study.

5. Conclusion

Based on the aforementioned observations and considerations, it can be concluded that the widely used RtR extrapolation methodology based on differences in (estimates of) absorption is not generally reliable and certainly not valid for substances inducing local effects. For many compounds a significant underestimation of toxicity is observed particularly where portal of entry toxicity is a factor. In contrast, for many other compounds the approach yields NOAELs that are much more than adequately protective. No reliable (quantitative) estimate of the uncertainty introduced by RtR extrapolation can be derived from the data analysis in this study because of the determined confounding factors. Although the present study is focussed on RtR extrapolation of oral to inhalation toxicity it cannot be excluded beforehand that the same conclusion holds for oral to dermal extrapolation as well.

More experimental data are required (e.g., from unpublished data or new experiments) to get insight into the reliability of RtR extrapolation and the possibility to derive an assessment factor to account for the uncertainties in this extrapolation. Moreover, for a reliable occupational health risk assessment validated screening methods to predict/exclude the occurrence of local effects after repeated exposure are warranted.

In view of the time and resources needed for the development of a sufficiently large database with route specific toxicity data and the development of predictive screening tests for local toxicity, route specific toxicity studies should be considered, in cases where chemical exposure by inhalation or skin contact cannot be excluded, to prevent from inadequate estimates of human health risks.

Acknowledgments

This study was funded by the Dutch Ministry of Social Affairs and Employment (SZW). More details on the analysis are described in TNO-report V97.520 ('Evaluation of route-to-route extrapolation in health

risk assessment for dermal and respiratory exposure to chemicals' by A. Wilschut, G.F. Houben, and B.C. Hakkert). This report is available upon request.

References

Alexeeff, G.V., Broadwin, R., Liaw, J., Dawson, S.V., 2002. Characterization of the LOAEL-to-NOAEL uncertainty factor for mild adverse effects from acute inhalation exposures. Regul. Toxicol. Pharmacol. 36 (1), 96–105.

Appel, M.J., Mommers, C., Muijser, H., Arts, J.H.E., Cnubben, N.H.P., Bessems J.G.M., Woutersen, R.A., 2003. Route to route extrapolation: comparison of sub-acute (28-day) toxicity of 1,4-dichlorobenzene in Fischer 344 rats after oral or inhalatory exposure (submitted).

Arts, J.H.E., Muijser, H., Appel, M.J., Bessems J.G.M. and Woutersen, R.A., 2003. Subacute (28-day) toxicity of furfural in Fischer 344 rats: a comparison of the oral and inhalation route (submitted).

Bos, P.M.J., Busschers, M., Arts, J.H.E., 2002. Evaluation of the Sensory Irritation Test (Alarie test) for the Assessment of Respiratory tract Irritation. J. Occup. Environ. Med. 44, 968–976.

De Raat, W.K., Stevenson, H., Hakkert, B.C., Van Hemmen, J.J., 1997. Toxicological risk assessment of worker exposure to pesticides: some general principles. Regul. Toxicol. Pharmacol. 25 (3), 204–210.

Dethloff, L.A., 1993. Route of administration and toxicity. In: Welling, P.G., Iglesia de la, F.A. (Eds.), Drug Toxicokinetics. Marcel Dekker, New York/Basel/Hong Kong, pp. 195–219.

Dourson, M.L., Felter, S.P., Robinson, D., 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. Regul. Toxicol. Pharmacol. 24, 108–120.

EC, 1998. Directive 98/8/EC of the European Parliament and of the Council of 16 February, 1998 concerning the placing of biocidal products on the market. Off. J. Eur. Commun. L 123, 24/04/1998: 1–63.

ECETOC, 1995. Assessment factors in human health risk assessment. Technical report no. 68, Brussels, Belgium.

EEC, 1991. Council Directive 91/414/EEC of 15 July, 1991 concerning the placing of plant protection products on the market. Off. J. Eur. Commun. L 230, 19/08/1991: 1–32.

EEC, 1992. Council Directive 92/32/EEC of 30 April, 1992 amending for the seventh time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Off. J. Eur. Commun. L 154, 05/06/1992: 1–29.

EEC, 1993. Council Regulation (EEC) No 793/93 of 23 March, 1993 on the evaluation and control of the risks of existing substances. Off. J. Eur. Commun., L 084, 05/04/1993: 1–75.

Gaylor, D.W., 1992. Incidences of developmental defects at the no observed adverse effect level (NOAEL). Regul. Toxicol. Pharmacol. 15 (2), 151–160.

Gerrity, T.R., Henry, C.J., 1990. Principles of Route-to-Route Extrapolation for Risk Assessment. Elsevier Science, New York.

Griem, O., Hassauer, M., Kalberlah, F., Oltmanns, J., Scheibner, J., Schneider, K., Schuhmacher-Wolz, U., 2002. Quantitative differences in xenobiotic metabolism between experimental animals and humans. Research Report Fb 963 of the Federal Institute for Occupational Safety and Health (BAUA: Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin), Dortmund/Berlin/Dresden.

Hakkert, B.C., 2001. Occupational Risk Assessment of Pesticides-Method used in the Netherlands for the setting of Acceptable Operator Exposure Levels. TNO report V4245, TNO Nutrition and Food Research Institute, Zeist, The Netherlands.

Muijser, H., Arts, J.H.E., Appel, M.J., Woutersen, R.A., 2003. Subacute (28-day) toxicity of captan in Wistar rats: a comparison of the oral and inhalation route (submitted).

Paulussen, J.J.C., Mahieu, C.M., Bos, P.M.J., 1998. Default values in occupational risk assessment. TNO report V98.390, TNO Nutrition and Food Research Institute, Zeist, The Netherlands.

Pepelko, W.E., 1987. Feasibility of route extrapolation in risk assessment. Br. J. Ind. Med. 44 (10), 649–651.

Pepelko, W.E., Withey, J.R., 1985. Methods for RTR extrapolation of dose. Toxicol. Ind. Health Dec. 1 (4), 153–170.

Rennen, M.A.J., Nordheim, K., Houben, G.F., De Heer, C., 2002. Prediction of local irritant effects after repeated dermal and respiratory exposure to chemicals. Regul. Toxicol. Pharmacol. 36 (3), 253–261.

Sharrat, M., 1988. Assessing risks from data on other exposure routes. Possibilities and limitations of using toxicity data derived from one exposure route in assessing risks from other exposure routes. Regul. Toxicol. Pharmacol. 8, 399–407.

TGD, 2003. Technical Guidance Document on risk assessment in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No 1488/94 on risk assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market.

WHO, 1989. IPCS Environmental Health Criteria 79. Dichlorvos. World Health Organisation, Geneva.

WHO, 1991. IPCS Environmental Health Criteria 120. Hexachlorocyclopentadiene. World Health Organisation, Geneva.

WHO, 1994. IPCS Environmental Health Criteria 170. Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-based Exposure Limits. World Health Organisation, Geneva.

WHO, 1995. IPCS Environmental Health Criteria 168. Cresols. World Health Organisation, Geneva.