The Interdepartmental Group
on Health Risks from Chemicals

Guidelines on route-to-route extrapolation of toxicity data when assessing health risks of chemicals

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The Interdepartmental Group on Health Risks from Chemicals (IGHRC) aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals.

The Steering Committee of the Interdepartmental Group on Health Risks from Chemicals comprises participants from the Department for Environment, Food and Rural Affairs, the Department of Health, the Department of Trade and Industry, the Home Office, the Environment Agency, the Health and Safety Executive, the Food Standards Agency, the Health Protection Agency, the Medicines and Healthcare Products Regulatory Agency, the Pesticides Safety Directorate, the Veterinary Medicines Directorate, the Biotechnology and Biological Sciences Research Council, the Medical Research Council and the Natural Environment Research Council.

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Foreword

This document has been produced by the Interdepartmental Group on Health Risks from Chemicals (IGHRC) as part of its Phase II work programme (September 2003-September 2007). Following initial drafting, we consulted Government departments, agencies and their advisory committees in order to obtain as broad an input and consensus as possible. The following Committees provided input to the document:

- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
- Advisory Committee on Pesticides
- Advisory Committee on Hazardous Substances
- Veterinary Products Committee
- Expert Panel on Air Quality Standards
- Working Group on the Assessment of Toxic Chemicals

While these Committees support the general principles of the route-to-route extrapolation of toxicity data described in this document, responsibility for the content of the document remains entirely with the IGHRC.

This document is intended to provide general guidance to assist those undertaking toxicological risk assessments. We hope it will be read as a useful and worthwhile attempt to clarify what is a complicated area of toxicology.

Dr David R Harper
Chairman of the IGHRC
Chief Scientist, Department of Health

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Executive Summary

Assessment of the hazard to health of chemicals is usually based on data from experimental animals and related systems, often involving less than ideal data sets. In this regard, it is often the case that information is available for only one route of exposure, usually the oral route. However, the dermal or inhalation route of exposure frequently predominates in practice, and an assessment of the hazard to health posed by these routes of exposure is necessary. Ideally, information should always be available for the same routes of exposure as arise in practice, but this would require a considerable increase in the number of animal tests and is not practical for a number of reasons. Risk assessors are therefore frequently faced with a lack of route-specific toxicity data.

Currently there is very limited guidance available to risk assessors on route-to-route extrapolation. Key factors that need to be considered in order to have confidence in these extrapolations are discussed in this report. These include target organ dose, route-specific metabolic factors and the use of assessment factors to account for uncertainties in the extrapolation. A number of situations are described where route-to-route extrapolation would not be considered appropriate, for example where the toxic effect of concern is at the initial site of contact, or where there is substantial metabolism at this site. Another concern is when a chemical is rapidly metabolised in the liver following oral absorption, resulting in significantly lowered levels reaching the systemic circulation (the 'first-pass' effect). The limited data available on validation of route-to-route extrapolations are also discussed.

The aim of this document is to provide guidance on the extrapolation of toxicity data obtained from one route (usually oral), to other routes of exposure, specifically dermal or inhalation. Guidance is also given, although more briefly, on extrapolation from inhalation to the oral route. Flow diagrams are included to assist the reader, together with recommendations for default values that can be used in the absence of data.

Current use of route-to-route extrapolations of toxicity data by three UK regulatory bodies is included in an Annex.

1 Introduction

Risk assessment of the health effects of chemicals is based on assessing the hazard to humans and relating this to anticipated exposures arising from the use of a chemical. In most cases, hazard identification is based largely on experimental data from toxicity studies in animals, and related experiments, from which a toxicological profile of a chemical is derived. The results of the animal studies have to be extrapolated to humans using expert judgement.

For a number of reasons (see later), animal data will mostly have been obtained using the oral route of exposure. However, the dermal or inhalation routes of exposure may predominate in humans exposed to a chemical during use or via the environment, and risk assessments often need to be carried out for these routes of exposure as well as for the oral route. The lack of dermal and inhalation exposure data introduces another extrapolation step in the safety assessment process. It could be argued that information should always be available using the same route of exposure that arises from normal use of a chemical. However, this is often not practicable, particularly for some endpoints and when it is important to determine the hazard as well as the risk from a particular type of exposure[1]. It is always necessary to consider whether any additional animal testing to cover the different routes of exposure can be justified, or whether reliable data can be obtained by route-to-route extrapolation. A requirement for experimental data in all cases would result in a very large increase in the number of animals used in assessing the safety of chemicals, and this would not be ethically acceptable, or scientifically justified. Risk assessors are therefore frequently faced with having to use only the available information.

In the context of this document, route-to-route extrapolation is defined as the prediction of the total amount of a substance administered by one route that would produce the same toxic endpoint or response as that obtained for a given amount of a substance administered by another route. As noted above, most available animal data are obtained using the oral route and the extrapolations most commonly carried out are from the oral to the dermal or inhalation routes.

The general principles of such extrapolations appear straightforward, involving conversion of the total amount of a substance administered by the oral route into a systemic dose by allowing for absorption, and comparing the equivalent systemic doses following dermal or inhalation exposure after allowing for absorption via these respective routes. However, there are many uncertainties and pitfalls in such a simplistic extrapolation.

The following sections cover key issues that need to be considered when carrying out route-to-route extrapolations (Section 3), the criteria that have been proposed for carrying out such extrapolations (Section 4), validation of approaches to route-to-route extrapolation (Section 5) and the very limited existing guidance given to Regulatory Agencies (Section 6). Detailed guidance on oral to dermal, oral to inhalation and inhalation to oral extrapolations is given in Section 7. The Annexes include a list of acronyms, a glossary, and the current use of route-to-route extrapolations by the Environment Agency, the Health and Safety Executive and the Pesticides Safety Directorate.

[1] Some chemicals are essentially not taken up by the dermal route. Thus, if the normal route of exposure were dermal, potential toxic effects of ingestion or inhalation would not be found if only the dermal route were tested.

1.1 Aim of the document

This document outlines the key factors that need to be considered in route-to-route extrapolations of toxicity data, together with the criteria that should be met to enable confidence to be had in such extrapolations. Some generic recommendations are made, which should help those involved in assessing the health risks of chemicals when considering whether route-to-route extrapolation is appropriate in a specific instance. It is recognised, however, that substances need to be considered on a case-by-case basis with expert judgement.

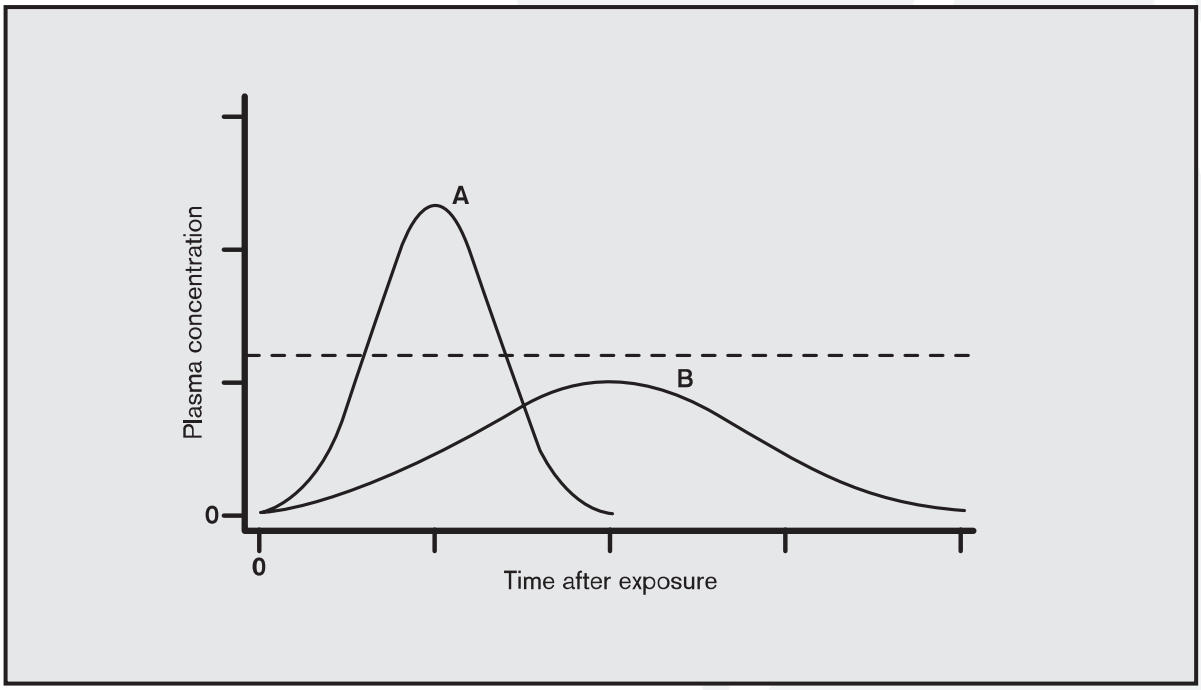
Because most available experimental data are obtained using the oral route, this document concentrates on extrapolation from the oral to the dermal or inhalation routes. Extrapolation from inhalation to the oral route is also considered. This is believed to cover all the situations likely to face risk assessors in practice. Exposure resulting from administration by the injection route (intravenous, intraperitoneal, etc.) is not usually considered, as it is not generally relevant to chemicals in normal use and in the environment.

Finally, the extent to which route-to-route extrapolations are currently used by regulatory agencies in the UK is described in an Annex.

2 The Need for Route-to-Route Extrapolation of Toxicity Data in Chemical Risk Assessment

As described in Section 1, risk assessors frequently have to use data obtained using a single route of administration. Most studies are carried out using the oral route (by gavage or in diet or drinking water)[2]. This is because such studies tend to be the most straightforward to perform and interpret, and dosimetry is easiest to quantify, particularly when a chemical is given by gavage. However, there may be differences between exposure via high 'bolus' systemic dosing resulting from administration by gavage and exposure via prolonged systemic dosing resulting from administration via food or drinking water or the skin. If the metabolism or action at the target site of a chemical is critically influenced by concentration at any one time, rather than by the total integrated systemic dose, the toxicity of that chemical may vary with route of administration or dosage regime if these affect the systemic concentration-time relationship. This is shown schematically in Figure 2.1.

Figure 2.1 Model of potential difficulties resulting from extrapolation from bolus exposure resulting from oral gavage to a prolonged exposure route such as dermal administration



Theoretical curves representing the plasma concentration of a chemical at different times of dosing. Curve A represents the systemic dose from a substance administered by gavage, which is rapidly absorbed. Curve B represents the systemic dose from a dermally applied substance that is slowly absorbed. In the model shown, the areas under the two curves are the same. However, if a removal mechanism becomes saturated at a plasma concentration shown by the broken line, the toxic effect in A will be greater than that in B, and extrapolation between the two routes will either underestimate (B to A) or overestimate (A to B) the hazard.

[2] Although not strictly a route-to-route issue, it is generally considered that intakes by gavage or diet or drinking water are equivalent on a dose to body weight (dose/bw) basis.

The toxicity of a chemical may also be altered by previous exposure, for example as a result of induction of metabolising enzymes. Although these effects of the dosing regime are important factors in the assessment of hazard, they are not specific to route-to-route extrapolation (for example, oral exposure is considered equivalent on a dose/bw basis whether the substance is administered as a single bolus by gavage or administered via the diet or the drinking water) and are not discussed in more detail in this document.

Studies of toxicity resulting from inhalation are technically much more complex. It is necessary to monitor the levels to which the animals are exposed and, in the case of aerosols and particulates, the particle size, in order to assess the amounts that penetrate the upper respiratory tract (inhalable) and the alveoli (respirable). Other factors that govern deposition include water solubility and reactivity. Calculation of dose is much more complex compared with using the oral route, being dependent on lung capacity, breathing rate, etc., as well as concentration and duration of exposure. The complexity of studies using the inhalation route (compared with oral studies) is reflected in the considerably more limited capacity of laboratories in the UK (and elsewhere) to carry out such testing, especially with regard to long-term studies.

Administration by both inhalation and dermal routes is also likely to be more stressful for the test animals than an oral study. In practice most available data are from studies using the oral route. This is not, of course, the case for gases, or for highly volatile organic liquids, where data will usually be available on toxicity resulting from inhalation but not from oral administration. It is rare to have any data other than that on acute toxicity for the dermal route of administration.

There is, therefore, commonly a need to extrapolate toxicity data obtained using the oral route of administration in order to assess human health risks resulting from dermal exposure or inhalation.

3 Key Considerations

A superficial consideration suggests that extrapolations from the oral to inhalation or dermal routes are straightforward, provided that adequate toxicity data are available using the oral route, and that data are also available on the extent of absorption through the lungs or skin. However, this is not the case, as there are a number of other factors to be considered before assuming that any toxicity seen following oral administration is representative of that likely by the other routes provided that the compound is absorbed to the same extent. There have been a number of reviews that consider the difficulties in such route-to-route extrapolations, and which emphasise the need to consider chemicals on a case-by-case basis with expert judgement (Pepelko & Withey, 1985; Pepelko, 1987; Sharratt, 1988; Gerrity & Henry, 1990). In all cases the desirability of having some toxicokinetic data was stressed.

The key factors that need to be considered are briefly summarised below.

3.1 Is the toxicity of concern a local or systemic effect?

Clearly compounds that have been shown to, or might be predicted to, act locally at the initial site of contact will express route-specific toxicity, and thus route-to-route extrapolation is not appropriate. This particularly applies to the case where irritancy is the concern and the effects are often dependent on the concentration present at the site of action rather than the systemic dose. Another area that presents difficulties is sensitisation of the immune system, where reactions are often route-specific. Furthermore, exposure by the oral route can sometimes lead to tolerance developing, resulting in reduced susceptibility to sensitisation by other routes of exposure.

For route-to-route extrapolation to be appropriate, the toxicological concern has to relate to systemic toxicity, that is, toxicity expressed in tissues/organs distant from the site of administration.

3.2 Target organ dose

Systemic toxicity is determined to a large extent both by the concentration of the toxic compound (which may be the parent compound or a metabolite) that reaches the target organ (i.e. the site of the toxic action) in the body and by the length of time over which the target organ is exposed to the toxic compound. This is dependent both on the extent of absorption and on the balance between any activation (where appropriate) and detoxification mechanisms. Thus the systemic toxicity may be the result of complex interactions, some of which could be route-specific.

Information as to whether the toxicity is due to the parent compound, or a metabolite, is valuable together with as much information as possible on toxicokinetics for all relevant routes.

3.3 Absorption as a determinant of target organ dose

The first stage in the passage of a chemical into the systemic circulation is absorption, and it is pertinent to consider briefly the main factors that govern the different routes under consideration. The barriers to absorption of a chemical differ markedly following exposure by the oral, dermal or inhalation route (TNO, 1998).

Metabolic processes, or other mechanisms affecting the integrity of a substance, may also be important in determining the target organ dose; these are considered later, in this document (see Section 3.4).

Oral absorption

Factors affecting the distribution of a compound following oral absorption have been reviewed (TNO, 1998; Tyler, 1999). Absorption can take place throughout the gastrointestinal (GI) tract, but the small intestine is particularly important because of the highly convoluted nature of its walls, resulting in a huge surface area available for

absorption. Absorption of organic compounds across the GI tract, from gut lumen to vessels draining the gut (veins, lymph ducts) is mainly by passive diffusion across the lipid membrane barrier formed by the bilipid structure of the cell membrane. This greatly favours the absorption of hydrophobic over non-hydrophobic chemical species and thus of non-ionised over ionised species. Some degree of solubility in the GI fluids is, however, important, and extremely lipid-soluble material (unless dissolved in oil) is less well absorbed. There are, of course, a variety of other transport mechanisms, but for organic xenobiotics these are usually quantitatively much less important.

The physical characteristics of the dosing formulation will also be important, with solutions tending to be better absorbed than suspensions. Any solvents and other components, such as surfactants, may also alter absorption.

Another important factor to take into account when considering the distribution of a chemical following oral absorption is that, from the lower oesophagus to the distal portions of the rectum, all absorbed material flows into a single vein, the portal vein, which is directly linked to the liver. This has implications regarding metabolism and the systemic availability of the compound (see Section 3.5).

Dermal absorption

The skin has a relatively small surface area for absorption compared with the GI tract or the lung, and this may be considerably reduced by clothing (TNO, 1998). Blood flow is relatively low, and the skin receives only about 10% of cardiac output. Furthermore, the diffusion pathway to the systemic circulation is relatively long (several cell layers compared with only two cell layers in the lung and GI tract). The rate-limiting barrier to absorption is the stratum corneum (the outer layer of the epidermis). Skin penetration depends mainly on passive diffusion through the lipid matrix between protein filaments (i.e. a lipophilic structure). After a chemical passes through the epidermis, diffusion through the dermis (a watery diffusion layer) is necessary before it reaches the systemic circulation. The rate of diffusion overall depends on the lipid solubility and the relative molecular mass of the chemical and, as with oral absorption, on the nature of any solvent or surfactants present.

In animal studies, the dermal application site must be covered to prevent ingestion of the chemical, and the extent of occlusion may affect absorption. Application rates are frequently well above those likely to occur in real-life situations, particularly near the limit dose, and the amount absorbed may be dependent on the concentration used. In addition, particularly in repeated administration studies, there are problems if the skin is damaged by any irritating/defatting effect produced by the compound itself; the relevance of such data to normal skin is then questionable (Wester & Noonan, 1980). It should also be noted that dermal penetration in the commonly used animal species tends to be higher than in humans.

For the reasons noted above, absorption through the skin is usually slower and less complete than through the GI tract or the pulmonary alveoli. The general factors that govern skin absorption are similar to those that apply to the GI tract, and compounds that are well absorbed through the skin will also be well absorbed orally.

Following absorption of a compound through the skin, most of it will enter the systemic circulation directly (unlike the situation following oral absorption).

Absorption following inhalation

Hext (1999) has reviewed factors affecting the absorption of a compound following inhalation. It is important in inhalation studies with aerosols/particulates to estimate the amount of substance that is respirable (as opposed to inhalable) and reaches the alveolar region of the lungs. Substances inhaled and deposited in the upper airways, before reaching the alveolar region, will tend to be transported via the mucociliary system and eventually swallowed, and so may still contribute to the body burden, but via the oral absorption pathway. In humans it is usually assumed that particles of less than 10 µm aerodynamic diameter can reach the alveolar region of the lungs, with optimum deposition around 0.01 µm (Figure 3.3.1). In the rat, particles of 4–6 µm or less can reach the alveolar region (Schlesinger, 1985).

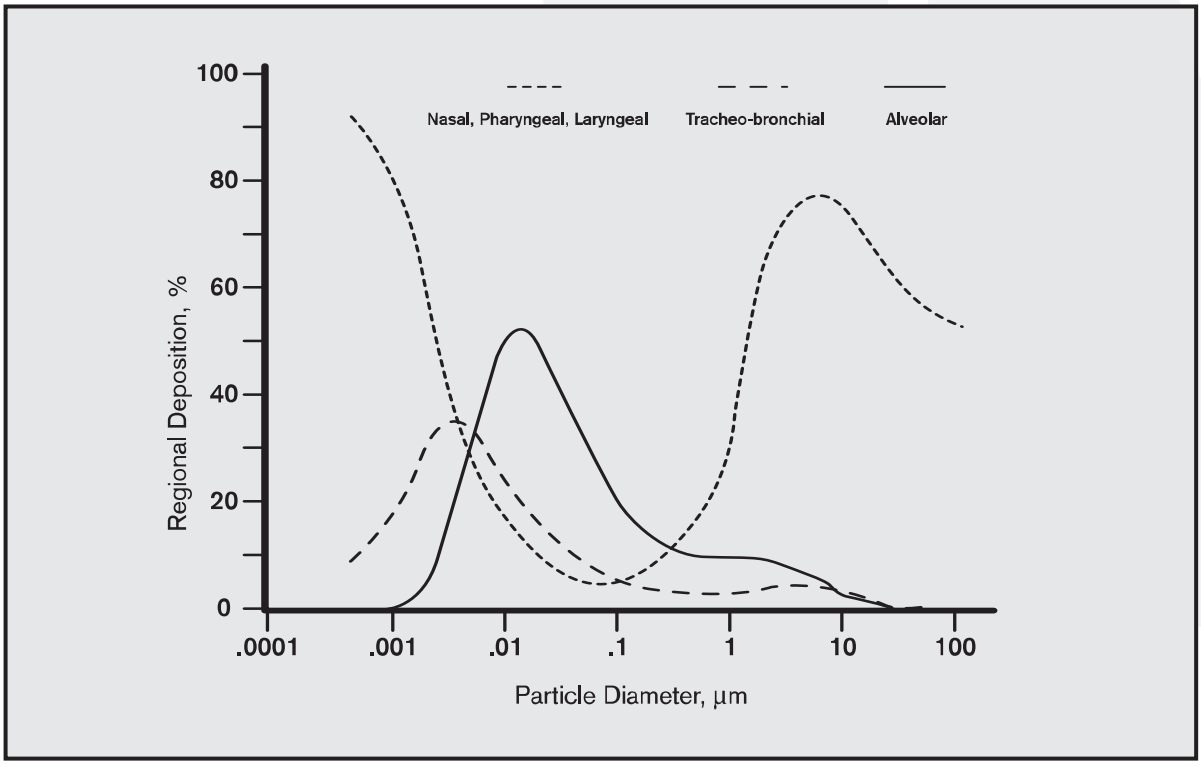
The alveolar region has a large surface area, and the distance between the blood and the alveolar air is only 0.2–0.4 µm. Absorption of gases and vapours from the alveolar region depends on the

blood/air partition coefficient. Highly reactive gases or vapours can react at the site of contact, and this will reduce the amount available for absorption. In practice, reactive gases and vapours are likely to cause toxicity at the site of contact and therefore would not be suitable candidates for route-to-route extrapolation. Absorption of particulates is dependent on solubility. Soluble particles depositing in the alveolar region can be rapidly absorbed by passive diffusion (as are gases and vapours reaching this area) whereas insoluble particles will not be absorbed to any significant extent, and instead will tend to accumulate. Such poorly soluble particles can have a long residence time in the alveolar region. Uptake can also be affected by any solvents and surfactants present. Blood flow to the lungs is high, and the total cardiac output passes through the lungs. These factors all tend to facilitate rapid absorption of chemicals that reach the alveolar region.

Substances that are absorbed through the pulmonary alveolar membrane enter the systemic circulation directly and pass through the heart into the general circulation before entering the liver.

Thus the factors that govern absorption though the lungs differ from those governing absorption via the GI tract. Provided that the substance reaches the alveolar region, it has much less of a barrier to absorption. Thus a compound may be poorly absorbed orally but well absorbed through the lungs. This is an important consideration when extrapolating from the oral to the inhalation route.

Figure 3.3.1 Model of deposition of inhaled particles of different sizes, in the upper and lower human respiratory tract



Source: International Commission on Radiological Protection (ICRP, 1994)

3.4 Route-specific metabolic factors

Metabolism specific to application site

In general, the biotransformation enzymes in extrahepatic organs are similar to those in the liver, but the distribution may differ, and there may also be differences in specific enzyme forms and their inducibility. Metabolism by extrahepatic enzymes has a minor effect on the overall disposition of a chemical, but metabolism at the absorption site could result in route-specific effects. This is considered in turn for the three sites of interest.

GI tract

Metabolism of a chemical can take place in the mucosal cells of the GI tract. These cells contain many of the phase 1 (cytochrome P-450) and phase 2 biotransformation enzymes also found in the liver, but activities in the whole tissue are usually much lower (Walsh, 1990). However, in rare instances the GI tract can be a major site of metabolism, for example the rapid inactivation of isoproterenol[3] by formation of ethereal sulphate in mucosal cells (1000-fold reduction in systemic availability compared with the intravenous route; Dollery et al., 1971).

Metabolism of a chemical can also result from the activity of intestinal micro-organisms (mainly anaerobic bacteria) in the large intestine (Rowland & Gangolli, 1999). An example is the production of cyclohexylamine from the intense sweetener cyclamate. Conversion into cyclohexylamine provides the basis for derivation of the acceptable daily intake (ADI) of cyclamate (EC, 2000). Anaerobic bacteria in the GI tract also have enzymes that have azo-reductase and nitro-reductase activity; these enzymes can reduce a wide range of azo-dyes to aromatic amines, some of which are carcinogenic.

Acid-labile chemicals may be broken down in the stomach before absorption in the small intestine. 1-Vinyl-2-pyrrolidone[4] is hydrolysed rapidly at the pH found in the stomach; it also polymerises readily and, although it is not known to what extent this occurs under physiological conditions, both hydrolysis and polymerisation may reduce the bioavailability of this substance (EC, 2003a).

The extent to which substances are, in practice, broken down (either enzymically or non-enzymically) in the GI tract is dependent on their solubility, and whether they are present as a solution or a suspension.

Skin

Although the skin contains many of the enzymes that occur in the liver and is capable of metabolising xenobiotics, levels are usually relatively low. The metabolising potential of skin has been estimated to be only about 2% of that of the liver (Pannatier et al., 1978). Others have suggested that the activity of biotransformation enzymes in the skin is similar to that in the lung (Bronaugh, 1990). Most activity is located in the epidermal layer of the skin.

It has been suggested that metabolism by the skin is probably too small to be worthy of consideration for most chemicals (Leung, 1999). Esterase activity may be an exception to this generalisation. A number of esters (e.g. parabens, retinyl palmatate) have been shown to be hydrolysed during skin penetration, thereby increasing systemic availability of the metabolites (Bando et al., 1997; Boehnlein et al., 1994).

Lung

Pulmonary tissue contains a range of microsomal oxygenase enzymes (containing flavin and cytochrome P450), although they are localised in a small proportion of cells. Their overall levels in the lung are, in general, much lower than those in the liver (Bond, 1990). These pulmonary enzymes have been shown to be important in the activation of lung carcinogens, such as some polycyclic aromatic hydrocarbons (IPCS, 1998). Phase 2 biotransformation enzymes are also present.

[3] Isoproterenol (isoprenaline) is a sympathomimetic agent acting as an agonist at beta-adrenoceptors. It is used in the treatment of cardiac disorders.

[4] 1-Vinyl-2-pyrrolidine is an organic liquid used predominantly in polymer production. The dose levels required to produce pathological changes in the liver by the oral route are considerably greater than those required by inhalation.

3.5 First-pass effect following oral administration

As noted earlier, essentially all of the compound that is absorbed from the GI tract following oral administration will enter the portal vein. It will thus enter the liver before reaching the systemic circulation.

If the compound is rapidly metabolised in the liver (usually by far the most important site, quantitatively, for the metabolism of chemicals) very little may reach the systemic circulation. If the compound itself, rather than a metabolite, is responsible for the toxic effects, this would result in a substantial lessening of toxicity by the oral route, relative to, for instance, injection routes. Exposure via the inhalation or dermal routes will avoid this first-pass effect. This probably explains why, for example, the organophosphates DEF (tributylphosphorotrithioate) and EPN (ethyl 4-nitrophenyl phenylphosphonothioate) are at least as toxic by the dermal as by the oral route, despite lower absorption by the former route (IPCS, 1986). In practice, however, the absence of a first-pass effect in the skin rarely has a significant effect on toxicity following dermal administration, because the rate of absorption through the skin into the systemic circulation will be appreciably lower than that through the GI or respiratory tracts. The compound will be rapidly metabolised in the liver, thus ensuring that blood levels remain low. Examples of compounds that are significantly more toxic by the dermal route than the oral route are very rare. For example, analysis of about 500 compounds notified to the HSE with base-set data under the Notification of New Substances Scheme, indicated that acute dermal toxicity data were only very rarely important for classification purposes. In only one case did the acute dermal toxicity data result in a more severe classification than the acute oral study indicated. Furthermore, the compound in question was classified as corrosive to the skin, and thus the integrity of the skin layer may well have been compromised, allowing much greater absorption than would normally be expected (HSE, personal communication).

In cases where the toxicity is due to one or more metabolites, rather than the parent compound, the above patterns will tend to be reversed. It is possible that greater toxicity will be observed by the oral route than by, for example, inhalation, because metabolites will more rapidly enter the systemic circulation. However, this will also depend on the extent of metabolic detoxification as well as activation, the overall toxicity reflecting the balance of the two processes.

4 Criteria for Route-to-Route Extrapolation

As described in Section 3, many factors must be taken into account when considering the appropriateness of using route-to-route extrapolation of toxicity data; each substance needs to be considered individually and expert judgement applied. Ideally there should be in-depth knowledge of the toxicokinetics and toxicodynamics of the test substance, together with information as to whether the compound itself or a metabolite is responsible for the observed toxicity. Physiologically based pharmacokinetic (PBPK) modelling data would be valuable and would obviate the need to use default values (see Section 7). Such data, however, will rarely be available for chemicals other than those used in the pharmaceutical area, and a pragmatic approach is necessary that recognises this fact.

It is important that any approach adopted is conservative, that is it errs on the side of caution. In the light of the large uncertainties in these procedures, over-prediction of toxicity is preferable to under-prediction. There is thus an asymmetry in the handling of uncertainty.

The following criteria have been proposed by Pepelko & Withey (1985) and Pepelko (1987) as a basis for deciding whether an adequate route-to-route extrapolation from the oral route can be performed, assuming that there are appropriate data from well-conducted studies using accepted methods (e.g. conforming to the OECD test guidelines):

- Absorption is the same between routes, or the difference is known and can be quantified;
- The critical target tissue is not at the portal of entry of the compound (i.e. the concern is with systemic toxicity and not local effects);
- There is no significant metabolism of the chemical by oral, gut or skin enzymes or in pulmonary macrophages, or transformation by other processes in the gut or lung;
- First-pass effects are minimal;
- The chemical is relatively soluble in body fluids.

An additional factor listed in the references cited is that the half-life of the chemical should be long. This presumably is proposed because a long half-life suggests that metabolism is low and therefore first-pass effects will be minimal. On this basis, the requirement for a long half-life is not an essential prerequisite for conducting a route-to-route extrapolation. As indicated in Section 2, the dosing method or regime may also alter the influence of first-pass metabolism on systemic toxicity.

With regard to the first criterion, absorption, conservative default values could be used in the absence of actual absorption data. It is noted that when extrapolating the no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) values based on administered doses to NOAEL/LOAEL values relevant to another route of exposure, it is more precautionary to assume that only a proportion of the administered dose was absorbed rather than 100%, that is, if the assumption is made that an adverse effect was caused by only 10% of the administered dose, this leads to a more precautionary NOAEL than assuming that 100% of the administered dose was absorbed. In contrast, when considering the amount of a substance that might potentially be absorbed for comparison against a NOAEL, it is more precautionary to assume that 100% of the administered dose is potentially systemically available. For these reasons, there may be asymmetry in the choice of default factors where measured data on percentage bioavailability are missing.

Some consideration is given in Section 7 as to what may be appropriate conservative default values for the various extrapolations, bearing in mind the need to avoid underestimating toxicity in the extrapolation process.

5 Validation of Approaches to Route-to-Route Extrapolation

In practice, despite the limitations noted in the previous sections, those involved in risk assessment of chemicals often carry out route-to-route extrapolations, and have to adopt a pragmatic approach to make the best use of the available data. This is usually done on the basis of the estimated absorption of a chemical across the respective routes (using default values in the absence of actual data). In addition, experimental data on acute toxicity by the relevant routes are sometimes available, which allows some assessment of relative acute toxicity across the routes of interest.

The reliability of route-to-route extrapolations based on the use of default values for absorption across the routes of interest has been investigated by a group at TNO in the Netherlands (TNO, 1998). The results of their work on extrapolation from the oral to the inhalation route have recently been published (Rennen et al., 2004). Because this appears to be the only published work on 'validation' of this approach it is considered in some detail below. In addition, their unpublished report (TNO, 1998) gives some limited data on oral to dermal extrapolation, which indicate less variability than with the oral to inhalation situation.

The reliability of extrapolation from an experimental NOAEL in a repeated oral administration toxicity study to an inhalation NOAEL, was investigated. The authors searched a fairly extensive database to obtain suitable studies (TNO archives on pesticides, data provided on priority chemicals in the EU Existing Substances Regulation, IPCS EHC[5] documentation, and JECFA/JMPR[6] assessments). Details of repeated oral administration toxicity studies were considered for 215 substances. However, pairs of studies of oral and inhalation repeated administration were available for only 28 compounds, and this included 10 compounds for which interspecies comparisons had to be carried out because the repeated administration studies were in different species. It also included eight compounds for which the toxicity was local, and it could be argued that these were inappropriate for consideration of route-to-route extrapolation. Thus the available data were limited and the conclusions are, as a result, less helpful than was hoped.

A comparison of the estimated inhalation NOAEL from the oral data with the experimentally-derived inhalation NOAEL was given based on the assumption of 100% absorption by both routes. Analysis of the data for the 20 compounds (i.e. the total group excluding those with site-of-contact toxicity) indicated estimated-to-observed ratios of less than one (i.e. the calculation method overestimated toxicity) in just over half the compounds (11/20, 55%). When all 28 compounds were considered this was, however, true for under half of the compounds (12/28, 43%). The range in this ratio was large (0.03–326) and covered four orders of magnitude, indicating the level of uncertainty involved.

The above results were based on the assumption of complete absorption by both routes. Modification of this to 75% or 50% by the various routes had little effect on the ratios. The authors stated that the large variability in the ratio of observed-to-calculated inhalation values could not be explained by differences in absorption.

The overall conclusion drawn by the authors was that extrapolation from the experimental oral NOAEL to an inhalation value was not generally reliable. They felt that much more experimental data would be needed in order to gain insight into the reliability of route-to-route extrapolation, or to obtain an assessment factor to account for the uncertainties in the extrapolation. In view of the time and resources needed to develop a sufficiently large database, it was felt that undertaking route-specific studies should be considered when there was human exposure by inhalation or dermal contact with a chemical.

[5] International Programme on Chemical Safety Environmental Health Criteria monographs.

[6] Joint FAO/WHO Expert Committee on Food Additives and Contaminants/Joint Meeting on Pesticides Residues.

However, as already indicated, many of the criteria listed earlier as being necessary in order to have confidence in such extrapolations were not adhered to (e.g. local toxicity with eight compounds) or their status was unknown (e.g. whether or not first-pass metabolism occurred). Furthermore, in many cases the 'paired' toxicity data were from different species, introducing another element of uncertainty. The number of compounds for which a proper comparison could be made was very small, probably only about ten. Furthermore, the influence of the dosing regime was not taken into account. It is considered that the limitations of the data used by Rennen et al. (2004) make it impossible to draw any definite conclusions about the use of route-to-route extrapolation.

5.1 Use of assessment factors

The data in the TNO (1998) report were considered in a review of the use of assessment factors in human health risk assessment of chemicals (Vermeire et al., 1999). This concluded that the following options could be considered to deal with the issue of route-to-route extrapolation of toxicity data:

- use of assessment factors to account for uncertainties in the route-to-route extrapolation; or
- use of repeated dose-toxicity studies with relevant exposure routes until validated and reliable route-to-route extrapolation methodologies become available. The role of PBPK modelling should be further investigated in this regard.

Vermeire et al. (1999) stated that the choice between these options was a regulatory one, depending on the level of reliability desired in the risk assessment. They also noted that the application of route-to-route extrapolation was heavily dependent on expert judgement.

Regulatory authorities/agencies often have to take pragmatic decisions on the available data, and it is not always possible for them to ask for additional testing to be performed; for example, they are frequently not able to ask for complex PBPK data.

A recent review by ECETOC (2003) of the use of assessment factors in human health risk assessment of chemicals came to similar conclusions to Vermeire et al. (1999). This is not surprising as the section on route-to-route extrapolation was based largely on the work of Pepelko's group (Pepelko & Withey, 1985; Pepelko, 1987).

The ECETOC recommendations regarding route-to-route extrapolation were as follows:

- route-to-route extrapolation is feasible only for substances with a systemic mode of action, and should take dose rate and toxicokinetic data into account;
- if route-to-route extrapolation implies a lower rate of dosing[7] this can be considered to provide a built-in safety margin. In such cases, no assessment factor is needed, that is, an assessment factor of 1 is considered to be appropriate;
- extrapolation from oral to dermal data may be considered on a case-by-case basis, provided that appropriate information is available on dermal penetration[8]. It is not appropriate to define a default assessment factor.

[7] In the context of the ECETOC report, 'lower rate of dosing' refers to a lower systemic concentration due to slower absorption; in practice this will apply only to the dermal route of exposure.

[8] With regard to the need for data in dermal penetration, it is noted in the text of the ECETOC review that quantitative structure-activity relationships, (Q)SARs, may provide an estimate of the percutaneous absorption rate within one order of magnitude.

6 Existing Guidance to Regulatory Agencies

Little information specifically on route-to-route extrapolations is currently available in the published guidance on risk assessments of chemicals. An exception is the EU Technical Guidance Document on risk assessment for new substances, existing substances and biocides, where there is a small section on route-to-route extrapolation (EC, 2003b). The importance of limiting any extrapolation to systemic toxicity is noted. Also the desirability of having some information on toxicokinetics is recognised, although the document is pragmatic and it is noted that data on kinetics and metabolism will frequently not be available and thus corrections can be made only for differences in bioavailability. Guidance is given on obtaining approximate dermal and inhalation NOAELs from experimental NOAELS derived from repeated administration by the oral route.

7 Guidance on Route-to-Route Extrapolation of Toxicological Data

This document has reviewed the need for, and the scientific basis underlying, route-to-route extrapolation of toxicological data. Key factors have been identified that need to be considered in order to have confidence in such extrapolations. The objective of this document is to produce some generic guidance in this area because currently very little guidance is available on the use of route-to-route extrapolations in risk assessment.

The following section presents a pragmatic approach that aims to minimise the need for animal studies and also to avoid the underestimation of toxicity. It is important to recognise that these generic considerations are intended to facilitate the process, but do not replace the need to consider chemicals on a case-by-case basis, with expert judgement.

7.1 Initial considerations

The following questions must be answered satisfactorily before a decision can be made to use route-to-route extrapolation of toxicity data for a chemical:

- Are there adequate toxicity data for one exposure route (usually the oral) to enable an appropriate risk assessment to be carried out for that route?
- Is the critical toxic effect[9] related to systemic effects rather than local effects at the site(s) of initial contact?

If the answer to either of these questions is no, then it is not appropriate to consider route-to-route extrapolation in that particular instance. If the answer is yes, then further consideration of this method is appropriate.

[9] Defined as the most sensitive and specific biological change that is outside acceptable physiological variation.

Consideration then needs to be given to whether there are any other impediments to the use of route-to-route extrapolation. For example, is there any evidence that the compound is metabolised (or broken down by non-enzymic pathways) to a significant extent at the initial sites of contact (i.e. the gut, respiratory tract or skin)? Also, is there evidence to indicate that the compound is subject to a significant first-pass effect following oral absorption due to rapid metabolism in the liver? If there is evidence that either of these situations applies then route-to-route extrapolation may not be appropriate. Information will be needed on whether toxicity is due to the parent compound or metabolites before any assessment can be made as to whether or not the extrapolation will result in a conservative estimate of toxicity or not. (In cases where, for example, a compound is given orally and is subject to a significant first-pass metabolism effect, and where toxicity is due to the parent compound, then extrapolation of toxicity by this route to the inhalation route may seriously underestimate the toxicity following inhalation, and this approach would thus not be conservative.)

The overriding principle in this guidance is to avoid situations where the extrapolation of data would underestimate toxicity resulting from human exposure to a chemical by the route under consideration.

In the absence of any evidence of the above concerns it may be assumed that route-to-route extrapolation is appropriate. This is considered below for the various scenarios likely to arise in practice in the risk assessment of chemicals.

7.2 Oral to dermal extrapolation

Extrapolation of toxicity data from the oral route of administration to the dermal route of exposure is the most straightforward as it offers less potential for underestimating the toxicity of a chemical. Such extrapolations are frequently carried out by those involved with industrial chemicals, pesticides or consumer products.

Amounts absorbed through the skin are usually lower than, or, at most, equivalent to, those absorbed through the GI tract. Furthermore, the rate of absorption is invariably lower. In both cases this assumes that the integrity of the skin is maintained and not compromised by any severe irritant/corrosive effects of the substance on the skin.

Even if the substance itself is the toxic agent and is subject to first-pass metabolism following oral administration, this is unlikely to result in a significant underestimation of toxicity by the dermal route, owing to the slower absorption and the rapid metabolism when the compound reaches the liver. However, one situation that would give rise to concern due to possible underestimation of toxicity is if the substance were subject to detoxification by breakdown in the gut, for example by the acidic gastric environment or enzymically; such breakdown would not occur using the dermal route.

Thus it is important to consider all the available data, with expert judgement, and not use the oral toxicity data to extrapolate to the dermal route when there is evidence that this could underestimate the effects of dermal exposure. In practice, however, such concerns are likely to be infrequent. Examples of compounds that have significantly greater toxicity by the dermal route (providing the integrity of the skin is not severely impaired) than the oral route are very rare. This is supported by data held by the Health and Safety Executive (HSE) under the Notification of New Substances Regulations, and by the Pesticides Safety Directorate (PSD) on pesticide approvals (HSE and PSD, personal communication).

Extrapolation from the data, based on an estimate of the relative bioavailability via the skin compared with the oral route, should thus be appropriate in most cases.

Ideally, information on the percentage bioavailability by the oral and dermal routes will be available, and this should be used to convert the administered dose into a systemic dose. However, such data are not always available.

Where data from the oral route are being used as the starting point, if no data are available on oral bioavailability, it would be appropriate to assume that 50% of an orally administered dose is systemically available. The value of 50% is an arbitrary choice that recognises that the GI tract is designed to favour the absorption of ingested substances into the body but that, in most cases, not all of the ingested material will be bioavailable. Thus, in the absence of data, the assumption is being made that effects seen following oral administration have been caused by a fraction of the administered dose and not the entire administered dose. If there is evidence to suggest poor oral bioavailability, for example the substance is a poorly soluble particulate, then it may be more appropriate to assume that only 10% of the administered dose is systemically available.

If no data are available on skin absorption then the most precautionary default would be to assume 100% absorption by this route although, in reality, very few substances will cross the skin to this extent. It may be more realistic to assume that the bioavailability across the skin is no greater than the oral bioavailability; hence, in the absence of data on dermal bioavailability, the assumption could be made that dermal bioavailability equalled oral bioavailability. If there are data to suggest poor bioavailability via the skin (e.g. by comparison of the acute oral and dermal toxicity data in the same species, or data on structural analogues), a value of 10% may be appropriate. However, data can be obtained on skin absorption relatively easily, including the use of in-vitro methods (see OECD Guideline No. 428[10]), and it is desirable to use actual data rather than default values.

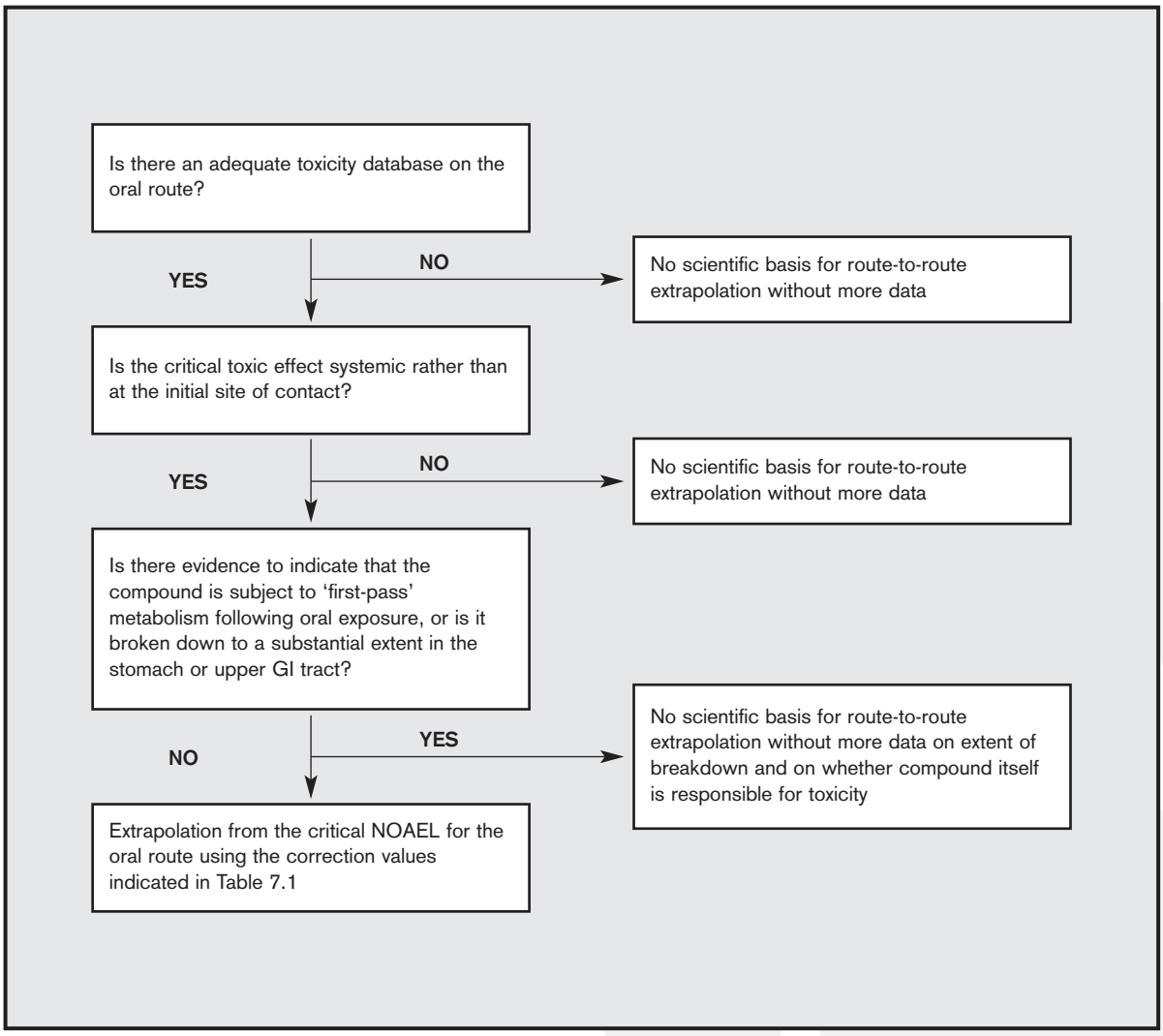
This approach demonstrates the asymmetric handling of uncertainty. Dermal absorption is normally lower than oral uptake and the default assumption is that they are the same, with a refinement to this value if there is supporting evidence. Where there are no data that allow refinement of the correction values, conservative default values can be used. This process is outlined in Figure 7.1, and the correction factors to be used are given in Table 7.1.

[10] OECD Guidelines for the Testing of Chemicals Test No. 428: Skin Absorption: In Vitro Method.

Table 7.1 Factors for deriving a dermal NOAEL from an oral NOAEL

Data available in addition to oral toxicity data	Multiply critical oral NOAEL by:
Oral and dermal bioavailability values	% oral bioavailability/% dermal bioavailability
Good oral bioavailability based on measured data or other information plus information suggesting that the substance will readily cross the skin	Assume equivalent bioavailability
Oral bioavailability data plus information from acute dermal toxicity or structural analogues indicating low dermal absorption	% oral absorption/10
Dermal bioavailability data plus information to suggest that bioavailability following oral administration will be good	50/% dermal bioavailability
Dermal bioavailability data plus information suggesting that bioavailability following oral administration will be poor	10/% dermal bioavailability
No bioavailability data by either route. The available information suggests no barriers to oral absorption but information from acute dermal toxicity or structural analogues indicates low dermal absorption	50/10
None	Assume equivalent bioavailability

Figure 7.1 Oral to dermal extrapolation



7.3 Oral to inhalation extrapolation

There is a greater potential for underestimating toxicity when extrapolating from the oral route to the inhalation route. The factors that govern pulmonary absorption differ from those governing oral absorption. It is possible for a compound that is poorly absorbed orally to be well absorbed if it reaches the lungs.

Inhaled substances may be in the form of a gas, vapour or airborne particles of liquids (aerosols) or solids. Because it is not possible to test gases by routes other than inhalation, gases will not be considered further. However, for a volatile liquid, it may at times be necessary to extrapolate from an oral study. If the volatile liquid is reactive, then it is likely to be toxic at the site of contact, and hence would not be a suitable candidate for route-to-route extrapolation. If there are no reasons to suspect that such toxicity will occur, then route-to-route extrapolation can be performed. Vapours, when inhaled, have the potential to reach all parts of the respiratory tract. In reality a proportion of any vapour that is inhaled will be exhaled unchanged. However, without actual data on percentage bioavailability it is difficult to quantify what this proportion will be. Therefore, in the absence of data it is most precautionary to assume that 100% of an inhaled vapour is potentially bioavailable.

The situation is more complex with airborne particles, as deposition in the respiratory tract depends on the particle size. In practice, human exposure scenarios usually involve a spectrum of

particle sizes. Particles with an aerodynamic diameter in the range 10-100 µm may be inhaled and reach the upper respiratory tract, but there is a low probability of their reaching the pulmonary region and they are considered non-respirable.
Such particles are most likely to be subject to mucociliary clearance from the upper respiratory tract and absorption from the GI tract after swallowing. Thus, although they will contribute to the total body burden, extrapolation of toxicity data from oral dosing studies is not problematic, because absorption will in practice be by the oral route. Hence, for a substance that is not respirable, the results from oral toxicity studies can be applied directly in an extrapolation to the inhalation route without the need to take account of bioavailability.

Respirable particles have the potential to reach the deep lungs and, once there, may be absorbed or retained for prolonged periods. It is therefore most precautionary to assume that 100% of respirable particles are potentially bioavailable.

This section sets out the particular considerations in using oral toxicity data to assess the hazard from respirable substances, that is, vapours and particles with an aerodynamic diameter below about 10 µm.

An important initial consideration is thus whether the substance will reach the pulmonary region of the respiratory tract. For particulates and aerosols the key factor in this regard is their aerodynamic diameter; in order for them to reach the alveolar region of the lungs this should be below 10 µm. Caution is needed in the interpretation of particle size data because measurements are often made on bulk material rather than the airborne fraction; it is the latter that is relevant to the estimation of exposure by inhalation. If it is not clear what proportion of the airborne material is inhalable and respirable then it is most precautionary to assume that all of the airborne material is potentially respirable.

Another consideration is the extent of absorption in oral toxicity studies. For the purpose of extrapolating between routes, if the substance has high oral toxicity it is often assumed that it is reasonably well absorbed by the oral route, but in certain cases this is not always true, for example paraquat. However, if the compound has moderate to low oral toxicity, this may either be because it has lower inherent toxicity or, alternatively, it may have significant systemic toxicity, but be poorly absorbed via the GI tract. It is the latter situation that is a particular concern as there is a real possibility that extrapolating from the oral to the inhalation route would significantly underestimate the effects of inhalation, and this would be counter to the general principle noted earlier of avoiding extrapolations that underestimate toxicity.

Thus for substances of low, and low to moderate, oral toxicity (e.g. those that are classified as harmful or not classified[11]), data are needed to estimate the extent of oral absorption. In the absence of experimental data on absorption it is necessary to have experimental data on acute inhalation toxicity, as well as by the oral route under comparable conditions (e.g. in the same species) in order that an assessment can be made of the relative potency by these two routes. This will entail converting the inhaled concentration into an absorbed dose (mg/kg) on the basis of the minute volume and percentage bioavailability, and then comparing the acute toxicity by the two routes, using lethality or another marker of acute toxicity. In this situation, a conservative default would be to assume equivalent bioavailability by the oral and inhalation routes.

As a pragmatic approach, the relative potency derived from comparison of the acute toxicities from the oral and inhalation routes can be used to estimate the NOAEL for repeated administration using the inhalation route, from the NOAEL derived from the repeated oral administration studies.

Where it is necessary to estimate inhalation toxicity from the results of oral studies without these additional data, it is suggested that, for substances that show high oral toxicity, a conservative approach would be to assume 50% oral bioavailability and 100% bioavailability by the inhalation route. For substances that show moderate or low oral toxicity it would be appropriate to assume 10% oral bioavailability and 100% bioavailability by the inhalation route. It is recognised that assuming 100% absorption by inhalation is likely to be an overestimate for

[11] For example, substances that produce evident toxicity only at about 300 mg or above in an acute oral toxicity test conducted according to OECD Guideline 420.

particulates/non-volatile aerosols, but this is in line with the general principle of avoiding extrapolations that would underestimate toxicity. Situations would need to be considered on a case-by-case basis and if there were data to indicate a more appropriate value, this could be used in the specific instance. Where there are no data that allow some refinement of the correction values, the default values given in Table 7.2 can be used.

Table 7.2 Default values for oral to respirable extrapolation

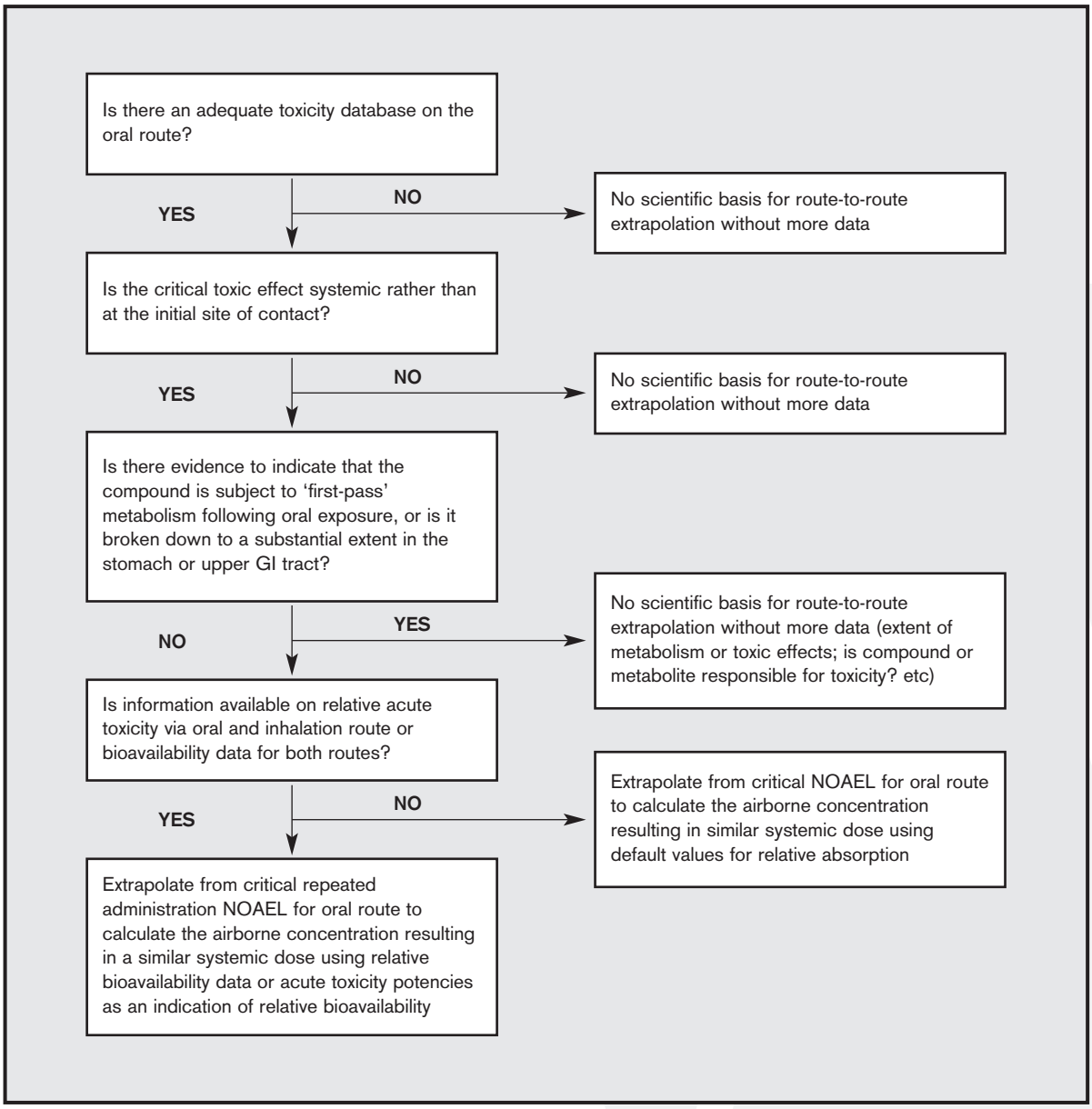
	Oral absorption %	Respirable absorption %
High oral toxicity	50	100
Moderate or low oral toxicity	10	100

Once again, uncertainty is dealt with in a way that biases the error towards over-caution. The process is outlined in Figure 7.2 and the correction factors are set out in Table 7.3.

Table 7.3 Factors for deriving a respirable NOAEL from an oral NOAEL

Data available in addition to oral toxicity data	Multiply critical oral NOAEL by:
Oral and inhalation bioavailability data	% oral absorption/% respirable absorption
Oral bioavailability; acute inhalation toxicity unknown	% oral absorption/100
Acute oral and inhalation toxicity data	Correction factor derived from a comparison of the relative potency in an acute oral toxicity study compared with an acute inhalation toxicity study.
Substance classified for acute oral toxicity as toxic or very toxic	
Bioavailability on inhalation	50/% bioavailability by the inhalation route
None	50/100
Substance classified for acute oral toxicity as harmful or not classified	
Bioavailability on inhalation	10/% bioavailability by the inhalation route
None	10/100

Figure 7.2 Oral to inhalation extrapolation



7.4 Inhalation to oral extrapolation

Extrapolation from the inhalation to the oral route is less likely to underestimate toxicity than when extrapolating the other way around. This is because pulmonary absorption is likely to be at least as great as absorption across the GI tract, and may be considerably higher. However, if there is a potential for the substance to be converted into a more toxic compound because of interactions with stomach acids or GI microflora, extrapolation from the inhalation route may underestimate systemic toxicity by the oral route.

The inhalation NOAEL needs to be converted into a systemic dose on a mg/kg body weight basis; 50% pulmonary absorption is used as the default values in these calculations. Again, this is an arbitrary choice that acknowledges that a proportion of an inhaled dose may not be bioavailable. Unless data are available on the extent of oral absorption, the default assumption to be used when extrapolating from the inhalation route to the oral route is 100%, which is a conservative approach.

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Annex A: Acronyms

AOEL
acceptable operator exposure level

CICAD
Concise International Chemical Assessment Document

CLEA
Contaminated Land Exposure Assessment

CLR
Contaminated Land Regime

COM
Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

COMAH
Control of Major Accident Hazards

DTL
dangerous toxic load

EA
Environment Agency

EASE model
Estimation and Assessment of Substance Exposure model

ECETOC
European Centre for Ecotoxicology and Toxicology of Chemicals

EHC
Environmental Health Criteria Documents

EINECS
European Inventory of Existing Commercial Chemical Substances

ESR
Existing Substances Regulations

EU
European Union

HCV
health criteria value

HSE
Health and Safety Executive

IPCS
International Programme on Chemical Safety (WHO)

JECFA
Joint FAO/WHO Expert Committee on Food Additives

JMPR
Joint Meeting on Pesticide Residues

LOAEL
lowest observed adverse effect level

MOS
Margin of Safety

NAEL
no adverse effect level

NOAEL
no observed adverse effect level

NONS
Notification of New Substances

OECD
Organisation for Economic Co-operation & Development

OEL
occupational exposure limits

PBPK
physiologically-based pharmacokinetic (modelling)

PPE
personal protective equipment

PSD
Pesticides Safety Directorate

(Q)SARS
quantitative structure-activity relationship

SCCPs
short-chained chlorinated paraffins

SGV
soil guideline value

SLOT
specified level of toxicity

TDI
tolerable daily intake

WHO
World Health Organization

Annex B: Glossary of Terms

The following glossary is included to provide the reader with a convenient set of definitions of toxicological and risk assessment terms used in government departments and agencies. The list is not intended to be exhaustive but to provide a level of inclusion sufficient to allow a clear understanding of terms and expressions used in this document or in common use in route-to-route extrapolations.

The definitions are based on those provided in government publications and in particular the Agency for Toxic Substances and Disease Registry (ATSDR) Glossary of Terms[12], the Joint OECD-IPC project on the Harmonisation of Hazard/Risk Assessment Terminology (2003)[13], the US EPA Terms of the Environment[14] and the International Programme on Chemical Safety (IPCS) Glossary of Terms for Use in IPCS Publications[15].
Other sources include the Society for Risk Analysis Glossary of Risk Analysis Terms[16] and the National Library of Medicine dictionary[17].

Term Description

Absorbed dose

The amount of a substance penetrating across the absorption barriers (the exchange boundaries) of the body, via either physical or biological processes

Acceptable daily intake (ADI)

The estimated maximum amount of an agent, expressed on a body mass basis, to which an individual in a (sub)population may be exposed daily over their lifetime without appreciable health risk

Acute toxicity

The ability of a substance to cause biological harm or death soon after a single exposure or dose; also, any toxic effect resulting from a single short-term exposure to a substance

The adverse effects occurring within a short time of administration of a single administration or multiple administration given within 24 hours

Adverse effect

The change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences

Assessment Factor

Numerical adjustment used to extrapolate from experimentally determined (dose-response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur

Bioavailability

The fraction of a chemical that can be absorbed by the body through the GI system, the pulmonary system or the skin and is systemically available

Biocide

A substance that is toxic to many different organisms

Biotransformation

The transformation of chemical compounds in a living organism

Body burden

The total amount of a substance in the body; some substances build up in the body because they are stored in fat or bone or because they leave the body very slowly

The amount of a particular chemical stored in the body at a particular time, especially a potentially toxic chemical, as a result of exposure

[12] Available [Feb 2006] at: http://www.atsdr.cdc.gov/glossary.html
[13] Available [Feb 2006] at: http://www.olis.oecd.org/olis/2003doc.nsf/LinkTo/env-jm-mono(2003)15.
[14] Available [Feb 2006] at: http://www.epa.gov/OCEPAterms/
[15] Available [Feb 2006] at: http://www.ilo.org/public/english/protection/safework/cis/products/safetytm/glossary.htm
[16] Available [Feb 2006] at: http://www.sra.org/resources_glossary.php
[17] Available [Feb 2006] at: http://www.nlm.nih.gov/medlineplus/mplusdictionary.html

Critical toxic effect

The most sensitive and specific biological change that is outside acceptable physiological variation

Dose

The total amount of an agent administered to, taken up by or absorbed by an organism, system or (sub)population

The amount of a substance available for absorption and subsequent interaction with metabolic processes or biologically significant receptors after crossing the outer boundary, i.e. skin

Dose rate

The dose (total amount of a substance administered) per unit time, for example in mg/day, sometimes also called dosage. Dose rates are often expressed on a per unit body weight basis, yielding units such as mg/kg/day. They are also often expressed as averages over some time period, for example a lifetime

Effect

A change in the state or dynamics of an organism, system or (sub)population caused by exposure to an agent

Evident toxicity

A general term describing clear signs of toxicity following the administration of a test substance. The international validation of a fixed-dose procedure as an alternative to the classical LD_{50} test such that, at the next highest fixed dose, severe pain and enduring signs of severe distress, or moribund status, or probable mortality in most animals, can be expected

Expert judgement

The opinion of an authoritative person on a particular subject

Exposure

The concentration or amount of a particular agent that reaches a target organism, system or (sub)population at a specific frequency for a defined duration

First-pass effect

The metabolism that an ingested compound undergoes in its passage through the gut and liver before reaching the systemic circulation

Gavage

Introduction of material into the stomach by a tube

Local effect

An effect involving or affecting only a restricted part of the organism

Minute volume

The volume of air breathed per minute: minute volume = tidal volume x respiratory rate

NOAEL

No observed adverse effect level

Relative potency

A comparison of the potency of two or more reference chemicals; the potency of a test chemical is reviewed at all levels of biological organisation (subcellular, cellular, animal, human)

Response

A change that develops in the state or dynamics of an organism, system or (sub)population in reaction to exposure to an agent

Risk assessment

A process intended to calculate or estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system

The risk assessment process includes four steps: hazard identification, hazard characterisation (related term: dose–response assessment), exposure assessment, and risk characterisation. It is the first component in a risk analysis process

Route-to-route extrapolation

The prediction of the total amount of a substance administered by one route that produces the same toxic endpoint or response to that obtained for a given amount of that substance administered by another route

Solution (dosing formulation)

A liquid containing a dissolved substance

Suspension (dosing formulation)

The state of a substance when its particles are mixed with but undissolved in a fluid or solid

Systemic dose

The total amount of an agent that is administered and subsequently absorbed into the body

Systemic toxicity

Toxicity expressed in tissues/organs distant from the site of administration

Tolerable daily intake (TDI)

The estimated maximum amount of a contaminant, expressed on a body mass basis, to which an individual may be exposed daily over their lifetime without appreciable health risk

Toxicity

An inherent property of an agent that causes an adverse biological effect

Toxicokinetics

The study of the time course of absorption, distribution, metabolism and excretion of a foreign substance (e.g. a drug or pollutant) in the body

Uncertainty

Imperfect knowledge concerning the present or future state of an organism, system or (sub)population under consideration

Lack of knowledge about variability in specific parameters in a risk assessment

Validation

Process by which the reliability and relevance of a particular approach, method, process or assessment is established for a defined purpose

Different parties define 'reliability' as establishing the reproducibility of the outcome of the approach, method, process or assessment over time. 'Relevance' is defined as establishing the meaningfulness and usefulness of the approach, method, process or assessment for the defined purpose

Annex C: Current Use of Route-to-Route Extrapolation by UK Regulatory Agencies

The use of route-to-route extrapolation by the Environment Agency

The Environment Agency uses toxicological data in assessing environmental risks to human health. These include risks from pollution of air, soils, surface waters and ground waters. Often, the Agency is able to use existing evaluations by authoritative expert bodies. These might be UK occupational exposure limits, EU drinking water standards or WHO tolerable daily intakes, for example, depending on the exposure scenario and controlling legislation.

Most of the Agency's current derivation of toxicological health criteria values (HCVs) is in support of the Contaminated Land Regime (CLR). The comments below are based on guidance for that regime (Defra & Environment Agency, 2002a,b), which was produced in consultation with the Department of Health and other government departments. Assessments are based on authoritative reviews and evaluations, and the Environment Agency consults with other government departments, particularly the Department of Health, in deciding appropriate toxicological criteria for a substance. This will include deciding on a case-by-case basis whether route-to-route extrapolation is appropriate.

Contaminated Land Regime

Assessing the potential risks to human health from land contamination requires integration of information on both the extent (and routes) of exposure and the toxicological hazard. Depending upon the land use and the physicochemical properties of the substance of concern, individuals using a site could be exposed simultaneously via a number of different exposure pathways (e.g. ingestion of soil, inhalation of gases and vapours, dermal contact). Because the Agency needs to assess risks from environmental contaminants, rather than marketed products, toxicological data relevant to the exposure route of interest can sometimes be sparse. Often, many of the available data are from studies using oral administration. Therefore, the types of route-to-route extrapolation that are used most often are: from oral route to inhalation route; and from oral route to dermal route.

In deriving an HCV, the Agency uses authoritative evaluations based on data for the relevant exposure route, if one is available. Route-to-route extrapolation is used with caution and on a case-by-case basis. The main factor considered in deciding whether extrapolation is appropriate is whether the critical endpoint is dependent upon the route of exposure: if it is, then route-to-route extrapolation is not considered appropriate. Extrapolation is clearly inappropriate when toxic effects are local to the site of exposure. For example, lung cancer is regarded as a risk from inhalation of nickel, but not from oral exposure (Defra & Environment Agency, 2003).

Route-to-route extrapolation to derive HCVs is appropriate only when exposure via different routes results in the same systemic toxic endpoint. In some cases, metabolism following exposure by different routes results in different systemic doses. In such cases there may be quantitative differences in toxicity via the oral and inhalation routes even though both types of exposure contribute to the same effect. For example, first-pass metabolism in the liver following oral exposure can be significant for some substances. These differences need to be borne in mind when considering route-to-route extrapolation.

The Agency's final decision on whether toxicological or epidemiological data generated using one exposure route can be extrapolated to derive an HCV for another route of exposure will be substance-specific, taking into account all available data and consulting with other government departments or expert bodies.

HCVs are compared with predicted exposures to soil contaminants in order to assess the potential risks to the health of individuals using a site. The Contaminated Land Exposure Assessment (CLEA) model estimates probable exposures via various different exposure pathways (Defra & Environment Agency, 2002b). The Agency uses the model to establish generic soil guideline values[18] (SGVs) to be used as intervention values in generic quantitative (Tier 2) risk assessments. For systemic toxicants – for which exposure via different routes would be expected to contribute to the same toxic effects – potential risks from all exposure pathways need to be considered together. Where there is only an HCV for one route of exposure (usually oral) it is not considered sufficiently protective or precautionary to assess exposures only via this route. In such situations, therefore, it is assumed in the derivation of Soil Guideline Values that such exposures contribute additively to any adverse effect for which a Health Criteria Value has been determined for a single entry route (Defra & Environment Agency, 2002b).

Example 1: Tetrachloroethanes (Defra & Environment Agency, 2004a)

An oral tolerable daily intake (TDI_{oral}) was adopted by the Agency as the HCV for evaluating risks from land contamination by tetrachloroethanes. This was based on a 1998 International Programme for Chemical Safety (IPCS) evaluation published in a Concise International Chemical Assessment Document (CICAD)[19]. The effects evaluation was based on the induction of liver tumours in a study in which 1,1,2,2-tetrachloroethane was administered orally to mice. The IPCS noted: "although there may be substantial variations in toxicokinetics following exposure to 1,1,2,2-tetrachloroethane by different routes, available data are inadequate to quantitatively account for these differences in the derivation of guidance values". Therefore, direct extrapolation to inhalation exposure, with no correction for differences in toxicokinetics, was applied by IPCS. Similarly, the TDI_{oral} was also adopted as the HCV for inhalation exposure (TDI_{inhal}) under the Contaminated Land Regime.

Example 2: 1,1,1-Trichloroethane (Defra & Environment Agency, 2004b)

An interim TDI derived by the World Health Organization (WHO) under its programme to propose guidelines for drinking water quality was adopted as the TDI for oral exposure (TDI_{oral}) for the assessment of land contamination. The WHO evaluation was based on data from an inhalation study, as no suitable oral data were available and systemic toxicity was the concern. Because the TDI was based on inhalation data, it was also adopted as an inhalation TDI (TDI_{inhal}).

Example 3: Phenol (Defra & Environment Agency, 2003)

A TDI_{oral} for phenol was proposed based on advice from the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) that there is likely to be a threshold for the mutagenicity of phenol following oral exposure. There were no suitable inhalation data from which to derive an HCV for inhalation of phenol. However, route-to-route extrapolation was not used to derive an inhalation HCV because COM advised that there was insufficient evidence to support a threshold approach to establishing an HCV for inhalation and dermal exposures. Nonetheless, in the absence of HCVs for inhalation and dermal intakes, the SGV aims to ensure that the total intake by all three routes – oral, inhalation and dermal – does not exceed the oral TDI. In addition, intakes by the inhalation and dermal routes should be kept as low as reasonably practicable, because it is assumed that there is no threshold for the mutagenicity of phenol by these two routes.

[18] Soil guideline values are concentrations of contaminants in soil below which there will be no significant possibility of significant harm to human health, if the values are properly applied as part of a comprehensive risk assessment.

[19] Available [Feb 2006] at: http://www.inchem.org/documents/cicads/cicads/cicad03.htm

References

Defra & Environment Agency (2002a) Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans (CLR 9), Bristol, UK, Environment Agency

Defra & Environment Agency (2002b) The Contaminated Land Exposure Assessment Model (CLEA): Technical Basis and Algorithms (CLR 10), Bristol, UK, Environment Agency

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Defra & Environment Agency (2004a) Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans: 1,1,2,2-Tetrachloroethane and 1,1,1,2-Tetrachloroethane (TOX 16), Bristol, UK, Environment Agency

Defra & Environment Agency (2004b) Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans: 1,1,1-Trichloroethane (TOX 25), Bristol, UK, Environment Agency

The use of route-to-route extrapolation by the Health and Safety Executive

The HSE provides hazard and risk assessments for industrial chemicals falling under the scope of several regulatory programmes arising from UK and EU legislation. These include the Notification of New Substances (NONS) and Existing Substances Regulations (ESR), the setting of occupational exposure limits (OELs), the provision of land-use planning advice in relation to sites falling under the scope of the Control of Major Accident Hazards (COMAH) Regulations, and the assessment of non-agricultural pesticides/biocides. In these situations, the primary routes of exposure are the inhalation and dermal routes. However, the preferred route of exposure for toxicity testing is the oral route. It is therefore necessary on occasion for the HSE to use route-to-route extrapolation to reach its position on a chemical. It should be noted that the data available to the HSE and the opportunities to request additional data vary between programmes, and this influences the circumstances in which the use of route-to-route extrapolation is considered.

Notification of New Substances Regulations

The NONS regulations provide a framework for gathering data and undertaking risk assessment on those chemicals that meet the definition of a 'new' substance. These are chemicals that are not listed on the European Inventory of Existing Commercial Chemical Substances (EINECS) and are not in the categories specifically excluded from the regulations (e.g. pharmaceuticals). The data requirements laid out in the regulations are related to the level of supply (in metric tonnes) of each chemical in the EU. At low levels of supply, below 1 tonne/year, the data requirements are limited to short-term toxicity data. When supply reaches 1 tonne/year, there is a requirement for the company supplying the chemical (called a notifier) to provide repeated dosing data, usually a 28-day oral dosing study. Longer-term studies are usually not considered until the level of supply reaches 10 tonnes/year or more. Notifiers are also required to submit a risk assessment for the chemical at each supply threshold. The HSE will assess these risk assessments for workplace exposure. The aim of the latter assessment is to identify the controls that are needed to ensure worker safety rather than precisely to define NOAELs for different routes of exposure. Owing to the limited datasets available for chemicals supplied in amounts of 1 tonne/year or less, risk assessments for occupational inhalation and dermal exposures are likely to be based on route-to-route extrapolation.

Data to support the extrapolation are usually limited, particularly at the lower levels of supply. There are unlikely to be any experimental toxicokinetic data to indicate whether or not a substance will undergo first-pass metabolism. For the dermal route, limited toxicity data might be available to compare with results from oral dosing studies. No data are likely to be available for the inhalation route. For this reason, the assumption is made that there are no differences in the systemic effects of chemicals by different routes. There may be information to suggest that a substance will have local effects. For the dermal route, this could be obtained from a skin irritation study. For the inhalation route, predictions will have to be made

based on physicochemical data indicating that the substance has an extreme pH or, on evidence from toxicity studies, suggesting that the substance is corrosive or irritating to mucous membranes. Where local effects are expected, route-to-route extrapolation will still be performed to gain an appreciation of the potential for systemic effects. However, there would also be a requirement in the risk assessment for workers to wear appropriate personal protective equipment (PPE) to counter the potential for local effects. Thus rather than attempt to define a threshold for local effects, measures are put in place to minimise exposure by the inhalation and/or dermal routes.

The starting point for route-to-route extrapolations performed under NONS is the predicted level of inhalation or dermal exposure. Measured exposure data are rarely available at the lower tonnage thresholds, hence the UK EASE (Estimation and Assessment of Substance Exposure) model is used to estimate exposure. For the inhalation route, the predicted exposure level given in mg/m^3 will be converted into an equivalent body burden expressed in mg/kg, assuming (i) 70 kg body weight, (ii) that a volume of 10 m^3 of air is inhaled per 8-hour shift and (iii) 100% absorption. The assumption that 10 m^3 of air is inhaled allows for moderate physical activity to be carried out during the shift. For the dermal route, the predicted exposure level given in mg/cm^2 will be converted into an equivalent body burden expressed in mg/kg, assuming 70 kg body weight and 100% absorption. The total surface area that is exposed is based on default surface areas that depend on the types of task that are being performed. For example, a surface area of 840 cm^2 is used if just the hands are likely to be exposed. A surface area of 1980 cm^2 is used if the hands and forearms could potentially be exposed[20].

These estimated systemic body burdens are then compared with the dose levels used in the repeated oral dosing study to determine the margin between doses causing effects and predicted exposures.

[20] The default body surface areas used in risk assessments conducted under the NONS regulations and the ESR are listed in the Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances, 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.

Sometimes it may be possible to refine the dermal risk assessment if there are data (usually information on the physicochemical characteristics of the substance) to suggest that 100% absorption across the skin is totally unrealistic. In such cases a lower value of 10% may be used. Because this is a data-gathering programme, if the risk assessment raises concerns then notifiers can be asked to provide data, for example inhalation toxicity tests, dermal penetration studies and/or measured exposure data to refine the risk assessment.

Existing Substances Regulations

The ESR provide a framework for assessing the risks to health posed by existing chemicals. Existing chemicals are those listed on EINECS. Datasets for chemicals that come under the scope of the ESR are highly variable. However, the Regulations provide the authority for EU Member States to ask for additional data to be provided if it is not possible to carry out a robust risk assessment based on the data that are already available. The goal of the human health risk assessment is to identify whether current levels of exposure are acceptable and, if not, what additional measures need to be put in place to ensure that exposures to the chemical at work, via consumer products and as a consequence of its presence in the environment are adequately controlled. In order to make this judgement, it is necessary to have an indication of where NOAELs and/or LOAELs lie for the oral, inhalation and dermal routes of exposure to compare with predicted or measured levels of exposure.

Ideally, NOAELs and/or LOAELs will be identified using route-specific data. However, these are not always available and in the interests of animal welfare, additional animal testing should be requested only when there are no other scientifically-robust methods to obtain the information. Therefore risk assessments conducted under the ESR will use route-to-route extrapolation to fill information gaps if appropriate. This means that in practice, route-to-route extrapolation will be considered only when the health concerns are systemic. A route-to-route extrapolation would not be performed where there are concerns for site-of-contact effects. Also, in cases where there is evidence for first-pass metabolism by any route, or for route-specific metabolic activation (e.g. activation of a chemical by gut microflora), route-to-route extrapolation would not be performed.

Where it is possible to use route-to-route extrapolation, because the oral route is the preferred route for the conduct of toxicity tests, it is usually the case that the route-to-route extrapolation will be based on oral data. Rather than try to calculate a NOAEL or LOAEL for the inhalation or dermal routes from the oral data, risk assessments are based on a comparison of the body burdens estimated to arise from inhalation or dermal exposure with the internal body burden at the NOAEL indicated by the oral toxicity studies. Information on levels of exposure could be either measured or predicted using the EASE model. If data are available to quantify the percentage absorption for any route then this model will be used to estimate body burdens, otherwise it will be assumed that there is 100% absorption for each route. The exception is the dermal route. If information on the physicochemical characteristics of the substance suggests poor absorption, a lower default value of 10% absorption may be used. As is the case for risk assessments performed under the NONS Regulations, predicted inhalation exposure levels are converted into an equivalent mg/kg body burden, assuming 70 kg body weight and that a volume of 10 m^3 of air is inhaled per 8-hour shift. Predicted dermal exposure levels are converted into an equivalent mg/kg body burden, assuming 70 kg body weight and using the default surface area information given in the Technical Guidance Document (TGD).

Example: $C_{10–13}$ chloroalkanes
(Environment Agency & HSE, 2000)

The main uses of $C_{10–13}$ chloroalkanes (short-chained chlorinated paraffins; SCCPs) are in metal working fluids and sealants, as flame-retardants in rubbers and textiles, in leather processing and in paints and coatings. Short-term toxicity studies indicate that SCCPs are of low toxicity by all three routes. There is no evidence for site-of-contact effects at relevant levels of exposure, although there is evidence that repeated dermal exposure can cause skin dryness and cracking due to defatting. Repeated oral exposure studies indicate that SCCPs produce adverse effects in the liver, thyroid and kidneys in laboratory rodents. However, the effects in the liver and thyroid are caused by mechanisms known to be of no relevance to humans. The risk characterisation for SCCPs is therefore based on the NOAEL of 100 mg/kg/day for effects in the kidneys in rats. There is no information to indicate what the corresponding NOAELs for systemic effects are for the inhalation and dermal routes. Hence, the risk characterisation for these routes is based on route-to-route extrapolation.

Toxicokinetic data suggest that SCCPs are readily absorbed across the GI tract. There is no information to indicate whether or not SCCPs undergo first-pass metabolism. For the purposes of risk characterisation, it was assumed that 100% of an oral dose is systemically available, therefore the body burden corresponding to the oral NOAEL is 100 mg/kg. Information on percentage absorption across the skin is limited to a single in vitro study. The results suggest that SCCPs are poorly absorbed across the skin; data from structurally similar chemicals support this view. On this basis, it has been assumed that only 1% of a dermal dose is absorbed, hence, for each exposure scenario, the estimated mg/kg dose to the skin was divided by 100 to obtain a corresponding body burden.
For the inhalation route 100% absorption was assumed, hence, for each exposure scenario, the body burden represented the entire dose breathed in during an 8-hour shift. In order to determine the margin of safety (MOS) for each exposure scenario, the estimated body burdens for the inhalation and dermal routes were added together and this value was compared with the body burden of 100 mg/kg equating to the oral NOAEL.

Occupational exposure limits setting

OELs are legal standards that define adequate control of exposure by inhalation in the workplace. Given that OELs refer to inhalation exposure, the ideal situation is that OELs should be derived from studies involving inhalation exposure, either of humans or of experimental animals. However, there are few or no data available on inhalation toxicity for some chemicals, and in such cases it may be possible to use information from oral dosing studies to help to derive the value of the OEL. It is not appropriate to use oral data to derive an OEL for chemicals that are likely to exert local toxicity in tissues at the site of contact; examples of such chemicals would include acids, alkalis and chemically reactive compounds. Oral toxicity data for such chemicals cannot be used to predict quantitative exposure–response relationships for respiratory tract effects following inhalation exposure. For the purpose of OEL setting, where extrapolations are

performed from oral to inhalation exposure, a default body weight of 70 kg is used, and it is assumed that 10 m^3 of air will be inhaled over an 8-hour working day. This amount assumes that moderate physical activity is carried out.

Example: Propranolol (HSE, 1995)

Propranolol is a pharmaceutical used for the management of hypertension, angina and cardiac dysrhythmias. Information on the effects of propranolol is available from clinical experience and human volunteer studies, mainly conducted by the oral and intravenous routes, but includes one single-exposure inhalation study involving both non-asthmatic and asthmatic subjects. It was judged appropriate to use the oral data for propranolol for OEL setting because propranolol lacks any irritant/corrosive properties and would be regarded entirely as a systemic toxicant. One of the main effects of exposure to low doses is the induction of pharmacological effects due to, for example, reductions in resting heart-rate and blood pressure. Beta-adrenoreceptor blockade can also cause bronchoconstriction, seen mainly in individuals already predisposed to asthma, although some non-asthmatic individuals may undergo mild transient effects.

A major issue in the interpretation of dose–response relationships for propranolol is that nearly all of the available studies used bolus oral or intravenous doses that produce high transient blood levels. In contrast, the main route of exposure in the occupational setting is via inhalation of propranolol dust. Although it is likely that propranolol will be well absorbed across the respiratory tract directly into the bloodstream following inhalation exposure, it is considered that propranolol is likely to be less biologically active via this route compared with the oral and intravenous routes of exposure. This is because exposure to propranolol via the oral or intravenous routes tends to be to relatively high (bolus) doses whereas, in the occupational setting, exposure will be spread over a longer time period and will result in far lower peak levels. Once absorbed, most propranolol will be bound to blood proteins (and subsequently eliminated via the liver), and because intake via the inhalation route is more gradual, it is likely that much less of it will be biologically available than via parenteral routes. Furthermore, following oral dosing there is the possibility of a contribution to biological activity from active metabolites that do not appear to be formed following intravenous dosing, to which inhalation exposure approximates. Some support for the view that propranolol is less effective via the inhalation route is provided by the only inhalation study available in humans. No effects on resting heart-rate or blood pressure were observed following the administration of 9 mg of propranolol over a two minute period via an inhaler, whereas it was possible to detect small decreases in resting heart rate and resting systolic blood pressure following repeated oral doses of 5 mg given every 8 hours for a total of five doses.

To derive the OEL, the lower limit of the therapeutic range, 20 mg as a single dose, was taken as a convenient starting point. No significant adverse effects on health would be predicted at such a dose. For a worker to inhale this dose over an 8-hour period, assuming that a total of 10 m^3 of air is inhaled, the corresponding airborne concentration would have to be 2 mg/m^3. It was considered that this level of workplace exposure should not contribute significantly to the total dose for an individual who may be undergoing clinical management with propranolol. Given the long history of clinical medical usage of propranolol, and the extensive toxicological database, it was not felt necessary to apply an uncertainty factor to the OEL to take account of variability in human susceptibility.

Land-use planning in relation to industrial sites that come under the scope of the Control of Major Accident Hazards Regulations

The HSE has a role in the provision of land-use planning advice in relation to areas surrounding industrial sites that hold COMAH-defined threshold amounts of dangerous substances. The HSE uses quantified risk analysis to calculate the risks to an individual or community of being exposed to harmful levels of toxic substances arising from accidental releases. These calculations are based on the likelihood of a defined member of an affected population receiving an exposure equal to or greater than that required to produce a specified level of toxicity (SLOT). The SLOT represents a level of toxicity that would cause:

- severe distress to almost everyone;
- a substantial fraction of the population to require medical attention;
- some people to be seriously injured, requiring prolonged treatment;
- any highly susceptible people to be possibly killed.

In order to determine the atmospheric conditions that would produce the SLOT, a numerical constant called the dangerous toxic load (DTL) is derived, which expresses the relationship between time exposed and concentration of the toxic substance. The DTL is used to construct risk contours surrounding the COMAH site. Each risk contour encloses an area inside which there is estimated to be a specified numerical risk of experiencing exposure conditions equal to or more severe than those required to produce the SLOT.

Because the assessment relates to the scenario of an accidental release, the most appropriate data to use to derive the DTL are single exposure data. For pragmatic reasons, exposure conditions producing around 1% lethality in a group of experimental animals are usually taken to represent SLOT conditions. Inhalation lethality data are often available, but if they are not, and providing the main toxic effects are systemic rather than local, an extrapolation from experimental data for the oral, or another, exposure route is considered.
The extrapolation uses the default assumptions of a human body weight of 70 kg, a human breathing volume of 1.25 m^3 per hour, and 100% bioavailability by both routes. Usually there are no data to indicate whether or not a substance is more or less toxic by the oral route than by the inhalation route, and it is therefore assumed that there are no differences. If there are reasons to suspect localised effects in the respiratory tract (such data may be physicochemical data indicating that the substance has an extreme pH, or evidence from toxicity studies suggesting that the substance is corrosive or irritating to mucous membranes) then such a route-to-route extrapolation would not be performed. An extrapolation would also not be performed if there were other data indicating substantial differences in the toxicity for the oral and inhalation routes, and the extent of these differences could not be estimated. In these situations, a DTL cannot be calculated; it should be noted that the HSE has no powers to request additional toxicity data under this regulatory scheme.

Example: Nitroglycerine (unpublished)

Nitroglycerine is used as a pharmaceutical in the management of angina; it is also used in the explosives industry. It is classified in the Approved Supply List as very toxic by the oral, inhalation and dermal routes, and hence falls under the scope of the COMAH regulations.

Nitroglycerine is rapidly and extensively absorbed by the oral, inhalation and dermal routes. However, systemic bioavailability by the oral route is reduced because of first-pass metabolism and possibly also hydrolysis in the digestive tract. Data on the effects of inhaling nitroglycerine are limited but suggest that the main effects are systemic (headaches and reduced blood pressure due to vasodilation).
There is no information on inhaled doses that could lead to lethality. Although such data are available for the oral route, given that nitroglycerine is subject to first-pass metabolism, it is not possible to make a reliable extrapolation from these data to the inhalation route. Information is also available on doses causing lethality following intravenous dosing. Normally, the instantaneous nature of intravenous dosing rules this out as an appropriate basis from which to perform a route-to-route extrapolation. However, in the case of nitroglycerine, uptake into the bloodstream following inhalation is likely to be nearly instantaneous. It was therefore decided in this one case to base the DTL calculation on intravenous LD_{50} data.

Starting with the lowest intravenous LD_{50} of 19 mg/kg, this was converted into an equivalent inhaled concentration, assuming a body weight of 70 kg and a breathing rate of 1.25 m^3/h for a period of 10 minutes. The period of 10 minutes was chosen to reflect the instantaneous nature of intravenous dosing. Assuming no species differences in susceptibility, the equivalent human 10-minute LC_{50} concentration was calculated to be 6384 mg/m^3. This value was then used to estimate the 10-minute LC_1 and to derive the DTL corresponding to the SLOT conditions. In this example, because the DTL was based on intravenous data, the estimated SLOT conditions would be appropriate only for exposures of short duration, up to a maximum of 20 minutes.

Risk assessments for biocides/pesticides

The HSE is responsible for carrying out risk assessments for non-agricultural uses of pesticides/biocides. The procedures used and the circumstances in which route-to-route extrapolation will be considered are essentially the same as those described by the Pesticides Safety Directorate (PSD) for agricultural pesticides/biocides (see below).

References

Environment Agency & HSE (2000) Risk Assessment: Alkanes, C10-13, chloro- (European Union Risk Assessment Report Volume 4 - Final Report), Luxembourg, Office for Official Publications of the European Communities

HSE (1995) Propranolol: Criteria Document for Occupational Exposure Limits (EH65/18), Sudbury, UK, HSE Books

The use of route-to-route extrapolation by the Pesticides Safety Directorate

The PSD performs hazard and risk assessments for plant protection products (agricultural pesticides) under UK[21] and EC[22,23] legislation. The basic procedures are similar for both schemes. The aim is to determine whether a pesticide poses acceptable risks when used according to the approved conditions of use. For estimates of the risks to consumers of produce that has been treated with a pesticide, the sole consideration is oral exposure. For those applying pesticides (operators), or coming into contact with treated areas after application (workers), or members of the public exposed at the time of application or subsequently (bystanders), dermal and inhalation exposures are considered. In the case of operators, the assessment can include consideration of personal protective equipment or engineering controls (e.g. closed tractor cabs) to reduce exposures to acceptable levels.

The majority of data received by the PSD to support pesticide approvals are based on dietary studies on the active substance in the pesticide, covering an extensive range of durations (e.g. acute to lifetime) and endpoints (e.g. mutagenicity, carcinogenicity, reproduction, teratogenicity). Single-dose, LD_{50}-type, studies will normally be available for dermal and inhalation routes. There are triggers in the legislation for when repeat-dose dermal or inhalation studies should be performed (e.g. vapour pressure >10 mPa). Such dermal or inhalation studies will often be simple 28-day investigations in rats or rabbits, even when the critical oral endpoint is in a reproduction or developmental study or in another species (e.g. dogs). In such instances the route-specific data cannot be used directly in the risk assessment. Where the acute dermal or inhalation studies show increased sensitivity or toxic effects different from those produced by oral dosing, further investigations can be requested. For some compounds, studies to investigate the critical endpoint have been performed by all routes.

If appropriate route-specific data are not available then a route-to-route extrapolation will be performed. This is normally done by deriving a systemic reference dose (acceptable operator exposure level, AOEL) from the most relevant oral study (normally 90-day study unless a shorter duration study gives a lower value, e.g. developmental study) and comparing this with the estimated systemic dose from the dermal and inhalation components of the exposure based on a predictive model[24].

1 The AOEL is derived by correcting the most appropriate oral NOAEL for the degree of oral absorption (normally derived from a gavage toxicokinetic study) and applying an assessment (safety) factor (normally 100-fold). Additional considerations are whether to include the biliary component if the liver is not the primary target organ; and whether absorption from the diet at the NOAEL will be comparable with a gavage dose in a vehicle – the assumption is that absorption will be the same. For a small number of active substances in pesticides, toxicokinetic data are available by routes other than oral, and these would be considered as part of a route-to-route extrapolation.

[21] The Control of Pesticides (Amendment) Regulations 1997. Statutory Instrument No. 188.
[22] The Plant Protection Products (Basic Conditions) Regulations 1997. Statutory Instrument No. 189.
[23] Council Directive of 15 July 1991 concerning the placing of plant protection products on the market (91/414/EEC).

[24] PSD (1992) UK Predictive Operator Exposure Model (POEM) - A User's Guide.

2 Using the predictive model[24], the dermal and inhalation exposures will be estimated based on the physical form of the pesticide product and the patterns of use. The model includes data from a range of monitoring studies, together with default values for parameters such as breathing rates and working patterns.

The inhalation contribution is based on estimates of the concentration in the breathing zone, and assumes 100% respirable fraction and 100% absorption via the lungs. This is considered to incorporate a degree of conservatism because many particles will be trapped in the nose or ingested orally following mucociliary clearance, and volatiles could be exhaled.

The dermal contribution is determined by correcting the amount of pesticide impacting on the clothing for any protection afforded by the clothing to estimate the dermal exposure. The dermal exposure is then corrected for the degree of dermal absorption. Default values for dermal absorption are used in the absence of data: currently, for most compounds, a conservative default of 100% is used, but for high relative molecular mass (>500) or very high or low lipophilicity (log K_{ow} < _1 or > 4) compounds, a value of 10% is used. These defaults are based on those defined in guidance produced for use in EU assessments under directive 91/414/EEC[25].
For many pesticides, either in vitro and/or in vivo dermal absorption data will be available, and these are used in the derivation of a value for penetration through human skin. Human skin is considered to be penetrated less easily than the skin of experimental animals (normally rat or rabbit) and so, if there is no information on human skin, data from experimental animals will be used uncorrected. Where there are data on human skin in vitro, these will be used either directly or to correct results from in vivo animal studies.

The total systemic dose from both inhalation and dermal routes is then summed and compared with the systemic reference dose.

[25] EU (2004) Guidance document on Dermal Absorption. Sanco/222/2000 rev.7; available [Feb 2006] online at: http://europa.eu.int/comm/food/plant/protection/evaluation/guidance/wrkdoc20_rev_en.pdf

Issues raised in respect of this approach include the assumption that the oral route will be the most conservative route of exposure. For primary toxicants with extensive hepatic metabolism this has been questioned and, where there is evidence of extensive first-pass metabolism, route-specific data could be requested or some form of correction applied. The alternative to route-to-route extrapolation could involve the routine performance of tests using all routes of exposure, which would require increased numbers of animals.

Example: An organophosphate insecticide used inside buildings

The primary observed effect in rats, dogs or rabbits was inhibition of acetylcholinesterase.
The cholinesterase inhibition reached a plateau after several weeks' administration, but exhibited incomplete recovery even several weeks after the last exposure. Following a single exposure, cholinesterase inhibition was still evident 7 days after dosing. The latter property indicates that intermittent use may result in a cumulative effect, and a short-term AOEL based on a single dose study may not be appropriate. Dogs appeared marginally more sensitive than rats. The NOAEL of 0.3 mg/kg bw/day for erythrocyte cholinesterase inhibition from the 13-week and 1-year dog studies was used to derive a systemic AOEL that covers all exposure periods. Oral absorption is extensive (ca 90%) and no correction was required.
The default assessment (safety) factor of 100 was considered appropriate. The systemic AOEL was set at 0.003 mg/kg bw/day.

A dermal absorption value of 5% was determined, based on in vivo data in rats for the formulated product and for solutions containing >10% w/v of product. A dermal absorption value of 25% was considered to be appropriate for solutions containing between 0.5% and 10% w/v of product.

This assessment was in line with a dermal study in rabbits that gave exposures on 5 days per week for 3 weeks and had a NOAEL (derived using a benchmark dose technique) of 3 mg/kg bw/day. No repeat-dose inhalation data were available.

Although the product can be applied using either a brush or a sprayer, the following example provides details of the assessment for the spray application.

Bystander exposure

(i) At the time of application

The greater potential for bystander exposure will arise when application is as a spray. Owing to the low vapour pressure (<10^{-5} Pa at 25 °C) of the product, exposure to vapour is likely to be negligible, and bystander exposure will result primarily from drift. Such exposure is likely to be brief and at a low level. Direct measurements are not available for hand-held sprayers, and the estimate of simulated bystander exposure used data for field crop sprayers. In a typical case following a single pass of the sprayer, the mean potential dermal exposure was measured as 0.1 ml of spray on a bystander positioned at 8 m from the edge of the treatment area. Typical mean potential inhalation exposure was measured as 0.02 ml spray/m^3 (Lloyd & Bell, 1983)[26]. Assuming a spray concentration of 13.33 mg/ml, no exposure reduction from clothing, 5% dermal absorption for the spray solution, a heavy work respiratory rate of 3.6 m^3/h, 5 minutes exposure, 100% absorption and retention of potential inhalation exposure, and body weight of 60 kg, the estimated total systemic bystander exposure was calculated to be 0.0024 mg/kg bw/day (80% of the systemic AOEL of 0.003 mg/kg bw/day). This indicates that the risk to bystanders at the time of application is acceptable.

(ii) Subsequent to application

There is the potential for exposure to vapour following application. The low vapour pressure of the product (<10^{-5} Pa at 25 °C) indicates this is not likely to present a concern. This is supported by data from California, where monitoring of chlorpyrifos (vapour pressure 2.5 x 10^{-3} Pa at 25 °C) residues in air adjacent to an orchard following application with a boom sprayer, and with temperatures up to 42 °C, indicated that exposures to chlorpyrifos would be <0.01 mg/kg bw/day. The extreme nature of the conditions in the chlorpyrifos study and the much higher vapour pressure are predicted to result in exposures two or more orders of magnitude higher than with this product, and hence exposures are predicted to be within the AOEL.

Should any spray drift outside the confines of the building it might deposit on adjacent gardens, and individuals might become exposed through contact with such deposits. It is possible to estimate such exposures using spray-drift fallout values, and the approach used by the US Environmental Protection Agency to estimate residential exposure from contact with treated lawns. This approach indicates that a small child playing on a lawn would have an exposure of 0.000 02 mg/kg bw/day, which is <1% of the AOEL.

Operator exposure

Operator exposure resulting from the use as a structural spray treatment was estimated using the UK Predictive Operator Exposure Model (POEM), in conjunction with information from the German model on mixing/loading for wettable powder formulations. The model is programmed with information specific to the product: application equipment; concentration of active substance in the product; work rates; container size; personal protective equipment; dermal absorption. In the example given below, the estimates assume that an operator will use a 15-litre sprayer to apply 25 litres of spray solution made from 3 kg of product containing 0.3 kg of active substance, over a period of 20 minutes. With a 15-litre tank this will involve two mixing and loading operations. The product is classified as a skin sensitiser so the operator will be expected to wear gloves, faceshield and coveralls during mixing, loading and spraying, and to use respiratory protection during mixing and loading. Data indicate that about 5% of the dermal exposure will be absorbed. Because the predicted exposure for an operator (0.013 mg/kg bw/day) exceeds the systemic AOEL (0.003 mg/kg bw/day) this method of application is not acceptable and would not gain approval.

Worker exposure

Although the product label requires that application sites are out of reach of children, livestock and pets, it is possible that workers entering treated areas may be exposed via dermal contact with treated surfaces and from inhalation of vapour. Worker exposure to vapour is unlikely to be significant,

[26] Lloyd GA and Bell GJ (1983) Hydraulic Nozzles: Comparative Spray Drift Study (Unpublished report SC7704 by British Agrochemicals Association and MAFF-funded Operator Protector Group, Harpenden, UK); copies available from: information@psd.defra.gsi.gov.uk.

considering the low vapour pressure and the normal ventilation requirements of animal houses. Assuming a worker body weight of 60 kg and a dermal absorption of 5% for deposits on treated surfaces, a worker would require dermal exposure to 3 mg of product to achieve a systemic exposure equivalent to the short-term (occasional use) systemic AOEL of 0.003 mg/kg bw/day.
This corresponds to all of the product on a treated surface area of 3 cm^2 when the product is applied as a paint, or 30 cm^2 when it is applied as a spray. This extent of accidental contact with surfaces treated by brush may be possible, and additional labelling to guard against this is recommended.

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