


GENERIC RISK ASSESSMENT MODEL FOR INDOOR RESIDUAL SPRAYING OF INSECTICIDES

First Revision (February 2011)



WHO Pesticide Evaluation Scheme
Department of Control of Neglected Tropical Diseases
Cluster of HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases
&
Chemical Safety
Department of Public Health and Environment
Cluster of Health Security and Environment



**World Health
Organization**

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**DEPARTMENT OF CONTROL OF NEGLECTED TROPICAL DISEASES
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WHO PESTICIDE EVALUATION SCHEME
&
DEPARTMENT OF PUBLIC HEALTH AND ENVIRONMENT
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The department welcomes feedback on the guidelines and suggestions for improvement from national programmes, research institutions and industry in order to improve future editions.

Acronyms and abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BMD	benchmark dose
DDD	daily dietary dose
DFI	daily food intake
EC	European Commission
EC ₅₀	concentration having a 50% effect on test populations against a specific end-point
EFSA	European Food Safety Authority
ETR	exposure–toxicity ratio
EU	European Union
EUROPOEM	European Predictive Operator Exposure Model
GLP	good laboratory practice
guideline scenario	exposure scenario which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information.
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JMPM	Joint Meeting on Pesticide Management
JMPR	Joint Meeting on Pesticide Residues
lax standard scenario	tropical conditions are accommodated and no personal protective equipment other than light clothing covering the trunk only is assumed
LC ₅₀	concentration killing 50% of the test organisms
LOAEL	lowest-observed-adverse-effect-level
LOEC	lowest-observed-effect concentration
MRL	minimal risk level
NOAEL	no-observed-adverse-effect-level
NOEC	no-observed effect concentration
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure level
PEC	predicted environmental concentration
PNEC	predicted no-observed-effect concentration
PPE	personal protective equipment
PSD	Pesticides Safety Directorate
RfC	reference concentration
RfD	reference dose
RPE	respiratory protective equipment
TSD	tolerable systemic dose
TWAC	time-weighted average concentration
UF	uncertainty factor
UKPOEM	UK Predictive Operator Exposure Model
USEPA	United States Environmental Protection Agency

1. Introduction

Indoor residual spraying is the application of insecticides on the inside walls of dwellings in order to kill target insects that come into contact with the treated surface. Such insecticidal deposits are intended to remain active for an extended period of time. Indoor residual spraying is widely used to control the vectors of malaria and Chagas disease.

The equipment used for indoor residual spraying is typically a compression sprayer fitted with a fan-type nozzle and a constant flow valve. The World Health Organization (WHO) has published specification guidelines on equipment for vector control (WHO, 2006a). Procedures for indoor residual spraying are contained in a separate manual (WHO, 2007).

The formulations commonly used for indoor residual application of insecticides are wettable powders, suspension concentrates and water-dispersible granules. Water-soluble sachets for ease of handling and mixing in a spray tank are also available (WHO, 2007). Emulsifiable concentrates are generally not recommended for use in indoor residual spraying.

The requirements, procedures and criteria for testing and evaluation of insecticides for IRS of malaria and Chagas disease vectors are available from WHO (WHO, 2006b).

2. Purpose

This document provides a generic model that can be used for risk assessment of exposure to insecticide products applied as indoor residual sprays. It aims to harmonize the risk assessment of such insecticides for public health use in order to generate comparable data for their registering and labelling by national regulatory authorities. The assessment considers both adults and children (all age groups) as well as people in the following specific categories:

- those preparing the spray;
- those applying the spray;
- residents living in the treated houses;
- residents who participate in preparing and applying insecticides.

The structure of this document follows that of *A generic risk assessment model for insecticide treatment and subsequent use of mosquito nets* (WHO, 2004). Because risk assessment is a constantly evolving process, guidance is also subject to change. Readers are therefore advised to consider any newer guidance published by WHO and other authoritative sources.

A document discussing the issues related to use of insecticides for IRS, including criteria for substance selection, has been published by WHO (Najera & Zaim, 2001).

3. Background

It is recommended that risk assessments proposed for indoor residual spraying of insecticides are not conducted *de novo*; risk assessments that have already been generated for the pesticides in the regulatory context of crop protection can be used as a starting point. Preference should be for international assessments, followed by peer-reviewed regional or national assessments; risk assessments published in reputable journals would be a third possible source.

For each component of the risk assessment, the additional information – or modification of the existing assessment – likely to be needed will be identified and discussed. It is assumed that the generic guidance given here will be followed in parallel with one of the published regulatory schemes. These regulatory schemes are intended for guidance and none is wholly prescriptive; all state specifically that expert judgement is required. Similarly, expert judgement will be needed to determine the modifications needed to make published risk assessments from regulation of pesticides suitable for the specific task of risk assessment of indoor residual application of insecticides.

3.1 Probabilistic vs deterministic risk assessment models

Historically, exposure models have been based on point estimates. This deterministic approach has the advantage of simplicity and consistency. Risk characterization is relatively straightforward: the exposure estimate is compared with a health-based guidance value. One of the drawbacks of this approach is that it incorporates no information about the variability of the exposures. Likewise, there is no assessment of, or information about, the uncertainty in the exposure estimate.

The probabilistic technique offers a complementary modelling approach that incorporates variability of exposure. Probabilistic modelling uses distributions of values rather than single values. The advantage of the probabilistic technique is that it provides the probability of occurrence of exposure, which offers a sophisticated way of characterizing and communicating risk. Just as for deterministic models, however, the validity of the exposure estimate depends on the quality and extent of the input data and the reliability of the estimation algorithm.

Probabilistic methods have been used widely in North America in estimations of dietary exposure (for example, in estimates produced by the United States Environmental Protection Agency). Over the past few years, regulatory bodies and industry have also moved towards the use of probabilistic techniques in refining exposure estimates in occupational exposures (for example, in estimates produced by the United Kingdom's Pesticides Safety Directorate). The European Commission and the OECD (Organisation for Economic Co-operation and Development) Working Group on Pesticides have prepared reports on the use of probabilistic methods for assessing operator exposure to plant protection products. In addition, use of probabilistic methods has been proposed for effects assessment (both for hazard identification and for assessment factors).

Problems in using probabilistic techniques lie principally in the following areas:

- the difficulty of using the models;
- algorithm development;
- collection of good-quality input distributions;
- criteria for decision-making (what is an acceptable risk and what is not); and
- communicating the results to stakeholders.

Models that appear to be easy to understand and “user-friendly” will be published in the near future. Nevertheless, despite this apparent simplicity, it is critical that risk assessors and regulators remain fully aware of the pitfalls of modelling. They must have comprehensive knowledge of the principles of exposure assessment and the techniques used to describe the exposure and risk – and thus be able to ask the right questions. Probabilistic modelling could, however, be used as a special technique in more complex situations or when deterministic assessments have identified exposures of concern (higher-tier assessments) (Nordic Council of Ministers, 2007).

WHO encourages anyone using the models published here to consider the probabilistic approach as an alternative, especially when higher-tier assessments are needed. Sophisticated probabilistic models are also being developed for hazard characterization and may provide alternative ways of setting acceptable exposure levels in the future (WHO, 2009a).

3.2 Essential elements of a human health risk assessment model

Comprehensive presentations on the principles of risk assessment can be found elsewhere in the scientific literature (see, for example, WHO, 1999); only a short summary is given here.

Hazard is defined as the inherent capacity of a chemical substance to cause adverse effects in humans and animals and to the environment. *Risk* is defined as the probability that a particular adverse effect will be observed under certain specified conditions of *exposure* or use. *Risk characterization* is the process of combining hazard and exposure information to describe the likelihood of occurrence and the severity of adverse effects associated with a particular exposure in a given population. The entire process of hazard assessment, exposure estimation and risk characterization is known as *risk assessment*. Management of *uncertainties* related to all natural processes, including processes related to risk assessment, is an essential part of a valid, good-quality risk assessment.

The subsequent process of *risk management* considers the risk assessment in parallel with any potential benefits, socioeconomic and political factors, and the possibilities for risk reduction, and other issues that are relevant in making operational decisions on the acceptability of a particular level of risk.

Risk assessments involve three steps:

1. *Hazard assessment.* Hazard assessment comprises hazard identification and hazard characterization, i.e. identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects occur, and the dose/exposure levels below which no adverse effects are observed.
2. *Exposure assessment.* Exposure assessment may concern pesticide operators (applicators), residents of treated dwellings, bystanders, domestic animals, wildlife and the environment. Exposure should be assessed in a "guideline scenario", which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information. A "lax standard scenario", however, takes into account the fact that in reality these instructions are not necessarily followed completely. Conservative, high end-point estimates of the default distributions are used as defaults. No account is taken of intentional misuse. All relevant routes of exposure are covered.
3. *Risk characterization.* In the risk characterization step, estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situations.

The various chapters of this report deal with specific information demands, data sources, uncertainties, discussion on vulnerable or sensitive subgroups, selection of default values and the underlying assumptions, etc.

4. The human health risk assessment model

4.1 Hazard assessment

The purpose of human health hazard assessment is to identify:

- whether an agent may pose a hazard to human health; and
- the circumstances in which the hazard may be expressed (WHO, 1999).

It involves the assessment of all available data on toxicity and on mode of action, and the establishment of dose-response curves and the threshold dose below which the toxic effects are no longer observed. The principles of human health hazard assessment are discussed in greater detail elsewhere (e.g. WHO, 1999); they are largely, regardless of the class of chemic or its use pattern, differing only in, for example, data requirements. These principles have been summarized in an earlier WHO publication (WHO, 2004), which describes a generic risk assessment model for insecticide treatment and subsequent use of mosquito nets and which, with some updating, forms the basis for the current text.

4.1.1 Sources of data

Hazard identification is based on gathering and analysing relevant data on the possible effects of the insecticide on humans. These data may include both toxicological (animal testing) and human data. It is recommended that, when available, risk assessments that have already been generated for the insecticides, e.g. in the regulatory context of crop protection, can be used as a starting point. These risk assessments usually contain all the relevant

health hazard data available for the insecticide in question and are therefore important sources of data. Preference should be for international assessments, followed by peer-reviewed regional or national assessments; evaluations published in reputable, peer-reviewed journals are also possible sources.

Examples of this kind of authoritative evaluation are given in Table 1. Many can be accessed on the Internet, for example via OECD's eChemPortal (<http://webnet3.oecd.org/echempportal/>). When existing evaluations are used as a starting point, the original study reports should also be consulted if they are identified as critical to the risk assessment. Literature searches should be conducted for any new published data, and any relevant unpublished studies should be evaluated and considered.

4.1.2 Types of health hazard data

Human data

In the case of insecticides that have been in use for many years, human data on their hazardous properties may be available. These data include:

- case reports of accidental and deliberate exposures and poisonings;
- epidemiological studies, including occupational studies on those manufacturing or using the pesticide formulations in question, or general population studies;
- ethically approved volunteer studies examining mild, temporary effects of short-term exposure or toxicokinetics of the substance in a limited number of subjects.

Table 1. **Examples of authoritative evaluations that may be used as starting points for the risk assessment of indoor residual spraying**

Joint Meeting on Pesticide Residues (JMPR) – Monographs and Evaluations	http://www.inchem.org/pages/jmpr.html
International Programme on Chemical Safety (IPCS):	
– Concise International Chemical Assessment Documents	http://www.inchem.org/pages/cicads.html
– Environmental Health Criteria Monographs	http://www.inchem.org/pages/ehc.html
International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans	http://monographs.iarc.fr/
USEPA – Pesticide evaluations	http://www.epa.gov/pesticides/regulating/index.htm , or http://www.epa.gov/pesticides/reregistration/status.htm
Agency for Toxic Substances and Disease Registry (ATSDR) – Toxicological Profiles	http://www.atsdr.cdc.gov/toxpro2.html
European Food Safety Authority (EFSA) – Pesticide Risk Assessments	http://www.efsa.europa.eu/EFSA/ScientificPanels/efsa_locale-1178620753812_PRAPER.htm

Evaluation of the relevance of these studies to risk assessment and their advantages and limitations are discussed in greater detail elsewhere (e.g. WHO, 1999). In general, however, existing reliable human data on particular aspects of toxicity should take precedence over animal data in the risk assessment. Hazard information data are most often available only for active ingredients, but all available data on the formulation should be noted. The so-called non-active ingredients also present in insecticide formulations should be recognized and taken into account whenever possible. Exposure assessment, however, always considers formulations.

Experimental toxicity data

For many pesticides, the human database is very limited. In these cases hazard assessment is dependent on information from experimental animals and on in-vitro studies. For insecticides recently registered or reregistered for use by regulatory authorities, it is expected that comprehensive toxicology studies will have been conducted according to modern standards and good laboratory practice (GLP), using internationally accepted protocols for toxicological testing such as those published by OECD (OECD, 1987; http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788), or USEPA (latest update 2007: <http://www.epa.gov/ocspp/pubs/frs/home/guidelin.htm>). For older pesticides animal toxicity data may be limited and may not encompass modern requirements (unless they have been recently evaluated in regulatory programmes intended to review old pesticides).

Like other chemicals, public health pesticides used in indoor residual spraying have the potential to cause a wide range of toxic effects. To identify the critical effects of the insecticide in question, a range of toxicity studies is usually needed. Although test requirements may vary to some extent with the country or region or with the precise use of the pesticide, the range of tests normally needed for health risk assessment, for example in regulatory approvals of pesticides and biocides in OECD countries, is very similar (Table 2).

It should be noted that toxicity test data are usually available only for pure substances; that is, for the active ingredients or solvents used in insecticide formulations rather than for the pesticide formulations themselves. Sometimes, however, some acute toxicity tests may also be performed with an insecticide formulation to ensure that the acute toxicity does not differ from that predicted on the basis of the test or its individual components.

4.1.3 Range of toxicity tests normally required for pesticide approval

In addition to these general requirements, information on dermal absorption is valuable in assessing the health risks of insecticides used in indoor residual spraying because of the possible repeated dermal exposure of inhabitants of treated areas. Inhalation toxicity studies may be of value in the assessment of risks to operators who are subject to potential acute and repeated inhalation exposure.

Table 2. **Range of toxicity tests normally required for pesticide approval**
Note: Studies marked with an asterisk (*) may provide useful dose–response data.

<ul style="list-style-type: none"> • Toxicokinetic studies, usually in the rat, using single and repeat oral dosing, to give information on absorption, metabolism, distribution and excretion of the parent compound and its metabolites. • Acute toxicity studies, to define the approximate lethal doses by oral, percutaneous, and sometimes inhalation routes, and the effects on body weight, clinical signs and gross pathology produced at lower dose levels following single-dose administration. • Skin irritation studies • Eye irritation studies • Repeat-dose oral toxicity studies*, normally for a minimum of 90 days in both rat and dog, to identify effects on organs, tissues, blood cells, and blood and urine chemical analytes. • Repeat-dose dermal and inhalation studies*, of 28 or 90 days' duration, may sometimes be required. • Genetic toxicity studies, in vitro for gene mutation and chromosomal damage. If any in-vitro tests indicative positive results, in-vivo genetic toxicity studies should also be carried out. • Chronic oral toxicity and carcinogenicity studies*, in the rat and mouse, to assess long-term toxicity and tumour incidence. • Reproductive toxicity studies*, including a multigenerational study in the rat and developmental toxicity studies in the rat and rabbit, to assess effects on male and female reproductive capacity and effects on embryonic/fetal development. • Delayed neurotoxicity studies are required for insecticides with structures related to those known to cause delayed neurotoxicity, such as organophosphates. • For more recently approved substances, studies on developmental neurotoxicity, dermal penetration and immunotoxicology and other specialized studies* may have been performed.
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Absorption of the insecticide by inhalation and ingestion and through the skin should be estimated in the hazard assessment. If no chemical-specific data exist, default values of 100% for inhalation and ingestion and 10% for the dermal route is used. It should be noted that while residents are usually exposed to the product as sprayed, i.e., a diluted solution, operators may be exposed to both the diluted product and the undiluted formulation. Dermal absorption may be different for these two. Thus, for mixing and loading, the absorption rate of the non-diluted formulation is to be used, while for other dermal exposure, that of the diluted spray is more appropriate (EC, 2002; WHO, 2004).

4.1.4 Evaluation of the toxicity information

An experienced toxicologist should evaluate the range and quality of human and animal toxicity information available. Although all the toxicity tests described in the previous section are useful for assessment of the hazard potential of an insecticide used in indoor residual spraying, it must be recognized that not all such tests may have been performed, that not all the studies performed were of good quality, and that data are therefore valid for use in risk assessment only with restrictions. However, although good-quality studies may be missing for some toxic end-points, potential health

hazards can often be characterized by weight-of-evidence analysis. It is especially important to recognize possible critical data gaps that may make the assessment uncertain. If the database is poor, information on chemically-related compounds may be useful in the assessment.

The following points are of particular importance in evaluating the relevance of toxicological studies to hazard identification and risk assessment:

- Experimental design and quality of the critical study or studies. This includes, for example, purity of the active ingredient tested, physicochemical properties (stability, etc.), size of the study (number of exposure groups, group sizes, sex, etc.), suitability of the exposure levels used, duration of exposure, extent of toxicological and statistical evaluation, relevancy of the route of exposure to humans, and whether the study adhered to established guidelines and GLP (WHO, 1999).
- Nature of the effects seen; their severity and sites, and whether they would be reversible on cessation of exposure.
- Is it possible to identify dose-response relationship, no-observed-adverse-effect-level (NOAEL) and lowest-observed-adverse-effect-level (LOAEL)?

4.1.5 Insecticides not recommended for use in indoor residual spraying

Compounds meeting the criteria for carcinogenicity, mutagenicity or reproductive toxicity categories 1A and 1B of the *Globally harmonized system on classification and labelling of chemicals* (United Nations, 2009; http://live.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html) can be regarded as highly hazardous pesticides (JMPM, 2008). The Joint Meeting on Pesticide Management (JMPM, 2008) has issued a general recommendation that pesticides meeting the criteria for highly hazardous pesticides should not be registered for use unless:

- a clear need is demonstrated;
- there are no relevant alternatives based on risk-benefit analysis; and
- control measures, as well as good marketing practices, are sufficient to ensure that the product can be handled with acceptable risk to human health and the environment (JMPM, 2008).

It is suggested that this recommendation be followed in the case of indoor residual spraying as well. It is generally considered that compounds that are both genotoxic and carcinogenic are particularly likely to exert effects at very low doses: even if studies indicate apparent NOAELs, these should not be used for risk assessment. Moreover, an insecticide of high acute toxicity, meeting the criteria of classes Ia or Ib of the WHO recommended classification of pesticides by hazard (WHO, 2010), is not recommended for use in indoor residual spraying. However, it is the acute toxicity of the *formulation*, not just of the active ingredient, that should be taken into account, based on data relating to the formulation itself.

If both the active ingredient and the formulation have shown a high incidence of severe or irreversible adverse effects on human health or the

environment, use of that particular insecticide may not be acceptable (JMPM, 2008).

4.1.6 Other special considerations in hazard assessment

Interactions between insecticides and other constituents of the formulation

If two or more insecticides are used concurrently, possible toxicological interactions between those insecticides should be considered. Insecticides of the same class may produce additive toxic effects; organophosphates, for example, decrease acetylcholinesterase activity. Other forms of interaction include synergistic (supra-additive) or antagonistic effects, which may be caused by different classes of pesticides, for example because of metabolic interactions. Unfortunately, reliable information is often unavailable but knowledge of metabolic pathways or of receptor binding may sometimes help in identifying possible interactions.

Interactions may also occur between the active ingredient and the solvent used in the technical product. Moreover, impurities present in the technical product, e.g. in organophosphate products, may interact with the product and affect its final toxicity. Specification of technical material is thus of the utmost importance (see <http://www.who.int/whopes/quality>).

4.1.7 Dose–response assessment and setting of acceptable exposure levels

Dose–response assessment is an essential part of hazard assessment for deriving health-based guidance values and for the assessment of risks. Different methods are available (WHO, 2009a). The standard NOAEL approach can be regarded as a simplified form of dose–response analysis, identifying a single dose assumed to be without appreciable adverse effects (WHO, 2009a). An important alternative approach is the benchmark dose method, based on the calculation of benchmark doses at which a particular level of response would occur (WHO, 2009a). Use of these approaches in the setting of acceptable exposure levels requires knowledge of the assumed shape of the dose–response curve. For some end-points, however, such as endocrine disruption, the shape of the dose–response curve is not well understood, which limits use of these data in the risk assessment.

NOAEL approach

For most end-points it is generally recognized that there is a dose or concentration below which adverse effects do not occur; for these, an NOAEL and/or LOAEL can be identified. For genotoxicity and carcinogenicity mediated by genotoxic mechanisms, dose–response is considered to be linear, meaning that risk cannot be excluded at any exposure level.

The NOAEL and LOAEL values are study-specific dose levels at which no effects or minimal effects, respectively, have been observed in toxicity studies (or, in some cases, in humans). The study design and the sensitivity of the test system can have a significant influence on NOAELs and LOAELs, which therefore represent only surrogates for the real no-effect and lowest-effect levels. Dose-response data and NOAELs/LOAELs can be obtained from repeated-dose toxicity studies, chronic toxicity/carcinogenicity studies, reproductive toxicity studies and some specialized toxicity studies. Human

epidemiological studies, e.g. on occupationally exposed workers, may also provide useful dose-response data.

Different NOAELs/LOAELs are usually identified for different toxicities/end-points; they can be tabulated for each type of toxicity to help in the identification of the critical end-point and the critical study (WHO, 2004). The lowest relevant NOAEL/LOAEL value should normally be used for risk characterization and the setting of acceptable exposure levels. It should be noted, however, that critical effects may not always be the same for different exposure scenarios. For example, for scenarios involving high-level acute exposure to acutely toxic insecticide, such as spraying of the insecticide, acute effects and irritation may be taken as critical effects, whereas effects from long-term/chronic studies should be considered in setting of reference value for long-term low-level residual exposure of inhabitants via skin and hand-mouth contact.

The following additional points should be noted when identifying NOAELs/LOAELs for insecticides (WHO, 2010):

- If irreversible toxicity is noted in any organs at higher dose levels than that at which the critical effect occurs, these levels should also be noted in case they may be relevant to the setting of tolerable exposure limits or to prediction of possible additional risks that may be present if certain exposures are exceeded.
- In the case of insecticides such as carbamates and organophosphates, which act on specific and nonspecific cholinesterases, the dose levels that cause measurable effects, even if those effects are not considered "adverse", should be noted. For example, while inhibition of plasma or brain butyrylcholinesterase serves mainly as an indicator of internal exposure, a statistically significant inhibition of 20% or more of brain or red blood cell acetylcholinesterase is considered to be of clear toxicological significance (JMPR, 1998a).
- There may be studies in which the lowest dose tested is a clear effect level and in which it is not possible to identify either an NOAEL or an LOAEL. In these cases, this lowest dose should be tabulated, noting that LOAEL and NOAEL may be significantly lower. Alternatively, the method for derivation of benchmark dose can be used (see below).
- If the highest dose tested is without any effect, this dose may be tabulated as the NOAEL noting that the true NOAEL may be significantly higher.

Benchmark dose model

A benchmark dose (BMD) model may be used as an alternative to the NOAEL-based approach in setting acceptable exposure levels where appropriate dose-response data are available (WHO, 2009). Whereas a NOAEL represents a single dose assumed to be without appreciable effect, a benchmark dose is based on data from the entire dose-response curve of the critical effect (WHO, 2009). For end-points with an assumed threshold level, a BMD model can be used as a point of departure for setting acceptable exposure levels in the same way as a NOAEL is used to apply similar uncertainty factors as to the NOAEL. A BMD model may also be helpful in situations where there is a need for low-dose extrapolation, such as occurs in carcinogenicity mediated by a genotoxic mechanism when it is

considered that the dose-response is linear. Usually, BMD_{10} – representing a level with 10% response – is used as a starting point for low-dose linear extrapolation in these situations (WHO, 2009).

Setting tolerable systemic doses: the use of uncertainty factors

In the setting tolerable systemic dose levels (TSDs), critical NOAELs/LOAELs (or benchmark doses) are divided by uncertainty factors (UF) to account for variability and uncertainties.

$$TSD = N(L)OAEL/UF$$

A TSD is expressed in mg absorbed chemical/kg body weight per day.

Uncertainty factors should take account of uncertainties in the database, including interspecies and interindividual differences. Unless there are chemical-specific data to support the use of chemical-specific UFs (WHO, 2005a), the use of a default UFs to account for these uncertainties is a standard approach in the setting of TSDs. If the critical NOAEL/LOAEL is derived from an animal study, a default UF of 10 is usually recommended to account for interspecies differences (WHO, 1994; WHO 1999). A default UF of 10 is also used to account for interindividual differences in the general population (WHO, 1994; WHO 1999). Contributors to the overall UF are normally multiplied because they are considered to be independent factors; the most commonly used default UF for the setting of TSDs in the general population is therefore $10 \times 10 = 100$ (WHO 1994; WHO 1999). However, this default approach can be modified if appropriate chemical-specific toxicokinetic or toxicodynamic data exist that justify lower uncertainty factors (UFs) for interspecies or interindividual differences. Moreover, if chemical-specific toxicokinetic or toxicodynamic data suggest higher interspecies or interindividual differences, UFs should be modified accordingly. Further details on chemical-specific UFs may be found elsewhere (WHO, 2005a).

In some cases, the use of additional UFs is justified (Dourson, Knauf & Swartout, 1992; Vermeire et al., 1999; Herrman & Younes, 1999; Dorne and Renwick, 2005; WHO, 1999; WHO, 2005a). Situations in which additional UFs should be considered include the following:

- When LOAEL is used instead of NOAEL, an additional UF (e.g. 3 or 10) is usually incorporated.
- When an NOAEL from a sub-chronic study (in the absence of a chronic study) is used to derive a TSD for long-term exposure, an additional UF (often 10) is usually incorporated to take account of the attendant uncertainties.
- If the critical NOAEL relates to serious, irreversible toxicity, such as developmental abnormalities or cancer induced by a non-genotoxic mechanism, especially if the dose-response is shallow (WHO, 1999).
- When there are exposed subgroups, which may be extra-sensitive to the effects of the compound (e.g. neonates because of the incompletely developed metabolism).
- If the database is limited.

Smaller UFs may be considered in certain situations, including the following:

- If the NOAEL/LOAEL is derived from human data, the UF for interspecies differences need not be taken into account.
- If chemical-specific data on the toxicokinetics or toxicodynamics of the insecticide in either animals or humans are available, the default UF of 100 may be modified to reflect these data (see WHO, 2005a).

Types of acceptable exposure limits needed for the risk assessment of indoor residual spraying

Different reference doses/TSDs may be needed according to the type of insecticide; a TSD based on repeated or long-term exposure is usually the most relevant. For insecticides with marked acute toxicity, it is important, however, also to verify that the maximal daily exposure is acceptable; for this purpose, the tolerable systemic dose for acute exposure, TSD_{AC} (based on e.g. ARfD) is used (Solecki et al., 2005).

Repeated exposure

The long-term TSD is usually based on systemic effects observed in long-term studies and is expressed as mg/kg per body weight per day. For most insecticides, guidance values for long-term TSDs have already been set by international or national bodies; these include acceptable daily intakes (ADIs) set by JMPR or the European Union, reference doses or concentrations (RfDs, RfCs) set by the USEPA, and minimal risk levels (MRLs) set by the ATSDR. While preference in the risk assessment for indoor residual spraying should be the ADIs set by WHO, guidance values set by other authoritative bodies can be used, especially in the absence of WHO guidelines or when WHO guidelines no longer represent current knowledge.

Long-term TSDs are set on the basis of oral studies: chronic studies most commonly use the oral route and many values, such as the ADIs set by JMPR, are intended primarily to control pesticide residue intake through the diet. However, operators and inhabitants of insecticide-treated dwellings are also exposed via skin contact and – especially when spraying does not follow the recommended procedures – by inhalation. All exposure routes must therefore be taken into account in estimating the total systemic exposure. Specifically, it should be noted that the JMPR/JECFA ADIs usually presume 100% gastrointestinal absorption; if actual data are available, the TSD (representing absorbed dose) should be derived from the ADI by considering the gastrointestinal absorption. On the other hand, it is important that TSDs also protect against possible local effects, for example on the respiratory tract.

In route-to-route extrapolation, one further issue worthy of note is the possibility of first-pass effect in oral exposure situations (EU, 2006). Parent compounds absorbed into the circulation of the gut are rapidly transported to the liver and may be extensively metabolized before reaching the systemic circulation (and possible target organs). Thus, systemic concentrations of parent compounds may be higher following dermal or inhalation exposure than following oral exposure.

Operators who carry out indoor residual spraying are often local residents living in the area who are exposed to insecticides at work and at home. Although operators may be at risk of inhalation exposure, this is not a significant route of exposure for residents if WHO guidance is followed (WHO 2007). It is therefore critical to ensure that the insecticides used do not have significant local respiratory effects and that TSDs set for long-term systemic exposure are protective also towards possible respiratory effects.

Regional and national occupational exposure levels (OELs) may be available for public health pesticides. However, it should be noted that these values do not take into account skin exposure, which may be more significant than inhalation exposure in pesticide application. In addition, OELs are usually set on the assumption that the insecticide is used by adult, healthy workers exposed only for the duration of the working day or for shorter periods of time, and may thus reflect only the need to protect against local effects such as irritation. The UFs applied in setting OELs therefore tend to be much smaller than those used in setting guidelines for population exposure.

For these reasons, the same systemic TSD is recommended for operators as for the general population.

Short-term exposure

A guidance value for short-term (24-hour) dietary exposure to agricultural plant protection products has been set by JMPR especially for insecticides with significant acute toxicity such as acutely neurotoxic insecticides, including those with anticholinesterase activity (organophosphates and carbamates); these values are called acute reference doses (ARfD).

The acute reference dose (ARfD) is defined as the amount of a chemical, expressed on a body weight basis that can be ingested over a short period of time, such as one day, without appreciable risk to health (JMPR, 1998; Solecki et al., 2005). It is derived similarly to the long-term ADI, using relevant human or animal studies of acute or short-term dosing. The critical NOAEL from such studies is used to derive the ARfD by application of a UF. If the data are based on animal data, an overall UF of 100 is commonly used unless chemical-specific information is available that supports the use of a lower UF (see above).

For organophosphates and carbamates, inhibition of acetylcholinesterase in either red blood cells or brain, measured minutes to hours after dosing, is an appropriate parameter on which to base the guidance value for short-term exposure. For example, the ARfD for chlorpyrifos is based on a study in human volunteers, in which a NOAEL of 1 mg/kg body weight was identified for the inhibition of erythrocyte acetylcholinesterase activity. Since the study carried out in humans, no interspecies extrapolation was needed and an ARfD of 0.1 mg/kg was set using a UF of 10.

For indoor residual spraying, a tolerable systemic dose for acute exposure, TSD_{AC} , derived from e.g. the ARfD may be used in the risk assessment, notably for insecticides with significant acute toxicity, to take account of acute risks related to, for example, insecticide application, spillages and acute post-exposure oral exposure of residents.

For most of the common insecticides used for IRS, an ARfD from JMPR is available for the derivation of the TSD_{AC}. or JMPR has concluded that because of lack of significant acute toxicity, no ARfD is needed (JMPR, 2010) JMPR has also laid down principles for the derivation of ARfDs for agricultural pesticides (Solecki et al., 2005); these can be adjusted for insecticides used for IRS when no authoritative acute reference dose is available.

4.2 Human exposure assessment

Exposure algorithms, default values and unit exposures, which describe the relationship between operational conditions and exposure, are taken from *Standard operating procedures for residential exposure assessments* (USEPA, 1997a), *Exposure factors handbook* (USEPA, 1997b) and *Child-specific exposure factors handbook* (USEPA, 2008), different agricultural field-study databases and modelling approaches (European Predictive Operator Exposure Model (EUROPOEM, 2003); UK Predictive Operator Exposure Model (PSD, 2007)). The default values should be modified by the user of the models on a case-by-case basis and replaced with appropriate measured or otherwise improved point estimates or distributions, when applicable. Similarly, application of anthropometric and physiological datasets derived from the true target population, when available, is likely to lead to more accurate exposure predictions.

The ability of a pesticide to cause adverse health effects depends on the route of exposure (ingestion, inhalation, dermal contact), the frequency and duration of the exposure, the toxicity of the insecticide, and the inherent sensitivity of the exposed person. Exposure has also been seen to be strongly related to the actual amount of product or active ingredient handled and applied. Exposure assessment of indoor residual spraying therefore consists of several different scenarios for different target groups.

For the risk characterization, a total exposure estimate must be calculated by summing up all relevant exposure routes and pathways.

The exposure assessment described in this document should be considered as a first-tier approach. Whenever needed, higher-tier assessments with more complex methods should be used. For example, probabilistic risk assessment with quantification of uncertainties can be used to estimate risks in more detail. WHO has published guidance on exposure models and communicating uncertainties is available (WHO 2005b; WHO, 2008).

Among the residents of the sprayed houses, unborn and newborn babies and children are of special concern because of their pattern of exposure and possibly greater sensitivity to toxic chemical action. This document provides a rough means of assessing the risks to these sensitive groups, but additional, chemical-specific information is likely to greatly improve the accuracy of the risk assessment, especially in the case of unborn and newborn babies.

Another important area of uncertainty is the risk assessment of bioaccumulative active ingredients, such as DDT; chemical-specific information on the metabolism and toxicokinetics is crucial for accurate risk assessment.

Assuming that properly calibrated and well-functioning equipment is used for application and that instructions, including safety precautions, are strictly followed, the exposure in indoor residual spraying should generally be low. However, optimum conditions do not always prevail during the spraying operations, and risk assessments that assume appropriate equipment and strict compliance with instructions may lead to an underestimation of the level of exposure. Unintentional misuse, however, is very difficult to take into account in models, and similar problems arise in trying to include the effect of contaminated clothing, sweating of the skin, use of contaminated rags or towels to wipe the skin, etc. in the risk assessments. In most cases, these parameters are impossible to quantify. Situations related to misuse or accidents are mostly not covered by this document. Reusing pesticide containers and lactating mothers working as operators are, however, mentioned. These scenarios are to be taken into account in specific cases. They can be more reliably quantified than most misuse situations. Moreover, the model does not take account of concurrent use of the insecticides for agricultural purposes. If the user of the models has any knowledge that suggests usage of risky equipment or work patterns, he or she is strongly recommended to use that more case-dependent information as the source of default parameters.

It is the aim of this document to provide an estimate of the risks in:

- optimal conditions, *i.e.* the guideline scenario; and
- a lax standard scenario, which allows for some common deviations from the instructions

4.2.1 General parameters for exposure assessment

The parameters provided below are common in both operator and residential exposure assessments. It should be emphasized that more chemical-specific or case-specific data should always be sought and used when possible.

- Anthropometric and physiological input parameters (weight, skin surface area, ventilation rate, food and water consumption) were taken from the USEPA (2008) dataset (Table 3). This was selected, as it is based on large numbers of persons studied, is relatively new and covers all different age groups. Operators are considered to weigh 62 kg (median for females 16-21 yrs, USEPA, 2008) (Table 3). In specific circumstances, it may be appropriate to lower the default weight, but this is likely to be a realistic assumption in most cases and also covers most females.
- Adult residents are also assumed to weigh 62 kg. Risks are also estimated for children aged 6-11 years (assumed to weigh 32 kg), toddlers around 2-3 years (14 kg) and newborns (4.8 kg, birth to 1 month of age) (USEPA, 2008).
- The film thickness of a non-viscous liquid likely to be in contact with unprotected, immersed skin is assumed to be 0.01 cm after run-off; thus 9.3 mL is the maximum amount of liquid on hands of an adult (total surface area of hands 930 cm² see Table 3) (USEPA, 2008).

Table 3. **Anthropometric and physiological characteristics used in the model^a**

	Adult ¹	Child (6-11 years)	Toddler (2-3 years)	Newborn ²
Weight kg	62	32	14	4.8
Body surface m ²				
total	1.69	1.08	0.61	0.29
hands	0.093	0.054	0.032	0.015
arms	0.264	0.137	0.072	0.040
forearms	0.111 ³	0.058 ³		
legs	0.556	0.301	0.142	0.060
lower legs	0.189 ⁴	0.102 ⁴		
feet	0.123	0.078	0.043	0.019
head	0.135	0.136	0.087	0.053
Respiration rate m ³ /h ⁵				
sleep/nap	0.40	0.38	0.38	0.28 ⁶
sedentary	0.40	0.38	0.40	0.28 ⁶
light activity	0.89	0.90	1.0	0.66 ⁶
moderate activity	1.9	1.7	1.7	1.3 ⁶
Food consumption g/d	1100	1100	1000	
Water consumption L/d	2	1	1	

^a Source: USEPA, 2008

¹ (16-21 years, female)

² Birth to 1 month

³ 42% of the surface of the arms (USEPA 1997b)

⁴ 34% of the surface of the arms (USEPA 1997b)

⁵ 95th percentile of short term exposure value

⁶ birth to 1 year

Parameters for exposure assessment – operator exposure

The parameters provided below relate to the technical procedures for the application of indoor residual insecticides, to the formulation used, etc. These parameters are used exclusively for operator exposure assessment.

The procedure for indoor application of residual insecticides is detailed elsewhere (WHO, 2007). WHO has published specifications for the equipment used in such applications (WHO, 2006a). In this exposure assessment (guideline scenario), it is assumed that WHO recommendations and product label instructions are followed. WHO recommends that operators wear an overall for IRS.

In the lax standard scenario: tropical conditions are accommodated and no personal protective equipment other than light clothing covering the trunk is assumed.

Specific exposure scenarios are described below. The tasks that are considered to cause exposure to operators are:

- mixing and loading; and
- application of the insecticide product by spraying and washing and maintenance of the equipment.

- For the assessment of operator exposure to insecticides applied as indoor residual sprays, it is assumed that operators wear overalls during spraying. In the lax-standard scenario, tropical conditions are accommodated and no personal protection other than light clothing covering the trunk is assumed.
- The insecticides formulations commonly used in indoor residual application are solid formulations (e.g. wettable powders and water dispersible granules) or liquids (e.g. suspension concentrates and capsule suspension) applied after suspension/dilution in water. These products are available in bulk or in unit-dose packages suitable for an individual spray tank load. Unit-dose packages are expected to minimize operator exposure to the insecticide.
- Insecticides should be applied to give a uniform deposit on wall surfaces. This requires a constant flow of spray from a nozzle held at a set distance from the wall (WHO, 2007). Spray should not be directly applied overhead by spray operators. Application of insecticide to high surfaces such as ceilings may require the use of an extended lance.
- For the operator, the duration of exposure is assumed to be two rounds of insecticide spraying annually, working 8 hours a day, 6 days a week, with each round lasting over a period of 36 days. Out of an 8-h working day, it is estimated that the exposure time is 4 h: 120L/day divided by 0.75L/min = 160 min actual spray operation + 80 min other in-dwelling activity. This information is based on information provided to the WHO Pesticide Evaluation Scheme (WHOPES) by selected national vector-borne disease control programmes. As some spraying is done by villagers who are recruited and trained for spray application, the exposure needs to be combined with the exposure assessment of a resident.
- It is assumed that the correct maintenance procedures of the spray equipment are followed to ensure that no leakages occur during the spray operations. For example, that no leakages occur on the hands from the trigger valve.
- It is assumed that a single spray operator can apply 12 tank-loads of insecticide spray during a day. Each tank load is assumed to be 10 litres and the wall surface is treated with 40 mL of spray solution to 1 m² (WHO, 2007). The number of houses that can be treated in a day will depend on the total area of the sprayable surfaces. The area of the house may vary between 40 m² and 200 m²; the default dwelling size used in the calculations is 10 m × 10 m × 2 m (height). The extent of contamination during the filling of the tank is assumed to depend on the size of the insecticide product container and the diameter of the package opening; for package sizes ≤2 L, the exposure is estimated to be 0.01 L per tank load on unprotected (no gloves) hands (UK POEM data, PSD, 2010, see Table 4.). For solid formulations, USEPA data on standard operating procedures are used. Unit dermal exposure for wettable powders (WP) during mixing and loading according to USEPA standard operating procedures is 9.7 mg a.i./kg a.i., that for water dispersible granules (WG), 0.07 mg a.i./kg a.i., and water soluble bags, 0.04 mg a.i./kg a.i. (US EPA, 2009).
- The concentration of the spray liquid is to be checked from product labels or material safety data sheets.

Table 4. **Default values for potential hand contamination (mL/operation) during mixing and loading of a liquid pesticide formulation (no gloves used)^a**

Size of container and diameter of opening	Contamination of hands (mL/operation)
1 litre, any closure	0.01
2 litres, any closure	0.01
5 litres, narrow closure	0.2
5 litres, 45 mm or 63 mm closure	0.01
10 litres, narrow closure	0.5
10 litres, 45 mm closure	0.1
10 litres, 63 mm closure	0.05
20 litres, narrow closure	0.5
20 litres, 63 mm closure	0.05

^a Source: PSD, 2007.

- Inhalation exposure to insecticides used in vector control is often low due to the low volatility of the insecticides used (WHO, 2004; USEPA, 1997a; EU, 2000). During indoor residual spraying, and particularly when equipment without pressure regulation is used, aerosol with small droplet size (longer persistence in the air) may be generated, which may cause inhalation exposure. The risk of inhalation is considered significant when the compression sprayer is used at pressures of 3 bar or higher.
- In the guideline-case scenario, it is assumed that operators wear appropriate personal protective equipment (PPE), i.e. gloves, other protective clothing and respirators, according to the label instructions and relevant WHO manual – both when mixing and loading and when spraying. In the lax standard scenario, however, it is assumed that no PPE is used, which may be quite common in view of the likely climatic conditions in which indoor residual spraying is carried out. When full PPE (respirator, protective gloves, long-sleeved protective clothes) is used, an overall reduction coefficient of 0.1 (10%) is applied (EUROPOEM, 2003).
- Washing and maintenance of spray equipment may cause exposure to operators' hands. In the guideline case scenario, gloves are used provide 90% protection. In the lax standard scenario, it is assumed that no personal protection is used.
- Malfunctioning equipment (leaks, variable and intermittently high spray pressure, equipment with the outer surface contaminated with the insecticide), may lead to very high exposure both by inhalation and by the dermal (larger areas of skin exposed) route. **Such misuses are not covered in this risk assessment.**

Parameters for exposure assessment – residents

This risk assessment model assumes that WHO recommendations for indoor residual spraying are followed: that residents are not in the house during spray operations and that they stay out of the house until the spray has dried; that all furniture is removed while spraying is in progress, or at least covered with plastic sheets; and that food items are removed before applying the insecticide (WHO, 2007). In specific cases, using empty

insecticide containers may be taken into consideration. This is, however, clearly a misuse that is not relevant for most assessments.

It is assumed that adults and older children are exposed similarly, that is, via dermal route when touching contaminated surfaces in treated houses and by ingesting contaminated foodstuffs or water. Post-application inhalation exposure is considered negligible owing to rapid loss of airborne aerosol and low volatility. For highly volatile active ingredients such as selected organophosphates, which are not recommended for use in residual treatments, it may be relevant to estimate inhalation exposure. If the vapour pressure of the active ingredient exceeds 5×10^{-5} Pa in 20-25 °C, the inhalation route should also be taken into account¹. The use of contaminated insecticide containers for storing drinking-water or food may cause exposure via ingestion. For toddlers, hand-to-mouth behaviour may increase exposure. For newborn babies, breast milk is an additional and important source of exposure to some insecticides.

4.2.2 Algorithms used to estimate exposure and absorbed dose caused by indoor residual spraying of insecticides

Operator exposure

Mixing and loading insecticide formulation

In mixing and loading, inhalation exposure is not considered significant (unit exposures for solid formulations $\leq 5\%$ of those for dermal exposure).

Products may be solids or liquids. Default dermal exposure to liquid products is estimated to be 0.01 mL per a mixing and loading session provided that

¹ Exposure by inhalation of gaseous insecticide should be considered when the vapour pressure exceeds 5×10^{-5} Pa in 20-25 °C (i.e., the concentration in air at saturation \geq approximately $5 \mu\text{g}/\text{m}^3$). The exposure can be estimated from

$$\text{Predicted dose mg/kg/d} = \frac{1000 \times P \times MM \times INH \times TID \times A}{R \times T \times AER \times BW},$$

where Predicted dose = daily systemic dose, P = vapour pressure of the a.i., (pascal), MM = molecular mass, INH = respiratory volume/24h (default for adults, children, toddlers and infants, 16.5, 12.4, 9.5 and $3.6 \text{ m}^3/\text{d}$ (USEPA 2008), TID = Time spent indoors (default, 12 h), A = pulmonary absorption (default, 100%), R = gas constant ($8.31 \text{ J} \times \text{K}^{-1} \times \text{mol}^{-1}$), T = temperature in degrees Kelvin (default, 298), AER = air exchange rate rate/24h (default, 24), BW = body weight (see Table 3).

In case the volatilization rate from the sprayed walls can be estimated, a more precise estimate of the exposure may be achieved from:

$$\text{Predicted dose mg/kg/d} = \frac{0.04 \times TC \times ADV \times INH \times TID \times A}{AER \times BW},$$

where TC = target concentration on the wall (mg/m^2), ADV = average daily volatilization %.

the package size is ≤2L (Table 4). For solids, default values derived from USEPA standard operating procedures can be applied (US EPA, 2009).

Solid formulations

$$\text{Predicted dose} = \frac{UE_{\text{dermal}} \times ML \times PPE \times AbsD \times EF}{BW \times AT}$$

Where:

- Predicted dose = TWA systemic dose due to dermal exposure from solid formulations, in mg a.i./kg BW per day
- UE_{dermal} = unit exposure. Default value for wettable powder, 9.7 mg a.i./kg a.i., for water-dispersible granules (WG), 0.07 mg a.i./kg a.i., water soluble bags, 0.04 mg a.i./kg a.i. (USEPA, 2009)
- ML = amount of insecticide active ingredient mixed and loaded per day; 12 loads/day, 10 L tank, concentration of the a.i. in the spray, chemical-specific data
- PPE = Protection by PPE: guideline scenario = 0.1, lax standard scenario = 1
- $AbsD$ = dermal absorption of the non-diluted formulation, percent; the default value is 10%
- EF = exposure frequency, 6 days/week, 6 weeks per treatment round, 2 rounds per year (72 days)
- BW = body weight (62 kg)
- AT = averaging time, 1 year (365 days)

Liquid formulations

$$\text{Predicted dose} = \frac{VF_{\text{dermal}} \times CF \times PPE \times AbsD \times EF}{BW \times AT}$$

Where:

- Predicted dose = TWA systemic dose due to dermal exposure from liquid formulations, in mg a.i./kg BW per day
- VF_{dermal} = volume of formulation on hands (see Table 4) × number of daily operations (12)
- CF = concentration (g/L) of active ingredient in the formulation
- EF = exposure frequency, 6 days/week, 6 weeks per treatment round, 2 rounds per year (72 days)
- PPE = Protection by PPE: guideline scenario = 0.1, lax standard scenario = 1
- $AbsD$ = dermal absorption of the non-diluted formulation, per cent; the default value is 10%
- BW = body weight (62 kg)

- AT = averaging time, 1 year (365 days)

Application of insecticide formulation, and washing and maintenance of spray equipment

Inhalation exposure

The estimation is based on 40 mL of spray being applied per 1 m², which in a 10 x 10 x 2 dwelling means total volume of the spray of 40 mL/m² × 4 × 10m x 2m = 3200 mL.

0.1% of the sprayed active ingredient is assumed to be evenly distributed in the room (in a volume of 2 x 10 x 10 m³ = 200 m³),

In the guideline scenario, respiratory protection equipment is assumed to give 90% protection.

In the lax-standard scenario, no respiratory protective equipment is used.

$$\text{Predicted dose} = \frac{RPE \times CS \times CA \times BV \times AbsP \times EF}{BW \times AT}$$

Where:

- Predicted dose = systemic dose due to inhalation exposure to the aerosol, mg a.i./kg body weight per day
- RPE = protection factor of respiratory protective equipment; 0.1 for the guideline scenario, 1.0 for the lax standard scenario
- CS = concentration of the active ingredient in the spray mg/mL from the concentration of the a.i. in the formulation, and its dilution for the spraying.
- CA = concentration of the spray in the inhaled air. The breathing zone concentration of the spray is $0.001 \times 3200/200 \text{ mL/m}^3 = 0.016 \text{ mL of the spray/m}^3$.
- BV = breathing volume (US EPA, 2009) = 1.9 m³/h (See Table 3). During the 4 hours spent in the actual spraying during a workday, a total of 7.6 m³ of contaminated air is inhaled per day.
- $AbsP$ = Absorption from the respiratory tract. The default value is 100%
- EF = exposure frequency, 6 days/week, 6 weeks per treatment round, 2 rounds per year (72 days)
- BW = body weight, 62 kg
- AT = averaging time, 365 days

Dermal exposure

In a **lax-standard scenario**, hands are exposed to the spray aerosol during application, and to the spray liquid during washing and maintenance of the equipment.

In the **guideline scenario**, the sprayer is fully leak-proof, protective clothing is worn against the insecticide aerosol, and appropriate gloves are used during the spraying and the washing and maintenance of the equipment. PPE are assumed to provide 90% protection.

$$\text{Predicted dose} = \frac{PPE \times VS_{\text{dermal}} \times CS \times EF \times AbsD}{BW \times AT}$$

Where:

- Predicted dose = systemic dose due to dermal exposure, mg a.i./kg BW per day
- *PPE* = protection factor of protective equipment; 0.1 for the guideline scenario, 1.0 for the lax standard scenario
- *VS_{dermal}* = volume of spray on hands = 9.3 mL/hands during the day (Table 3).
- *CS* = concentration of the active ingredient in the spray mg/mL from the concentration of the a.i. in the formulation, and its dilution for the spraying.
- *EF* = exposure frequency, 6 days/week, 6 weeks per treatment round, 2 rounds per year (72 days)
- *AbsD* = dermal absorption, default = 10%
- *BW* = body weight, 62 kg
- *AT* = averaging time, 365 days

To estimate the maximal daily dose (for the assessment of acute toxicity by comparison to the TSD_{AC}), the total operator exposure is multiplied by AT/EF = 365/72 = 5.07.

Residential exposure

Residential exposure is assumed to be the result of dermal exposure to directly sprayed walls and sometimes from furniture, shelves and floors sprayed inadvertently. Furthermore, the sprayed insecticide may reach food items, loosen from walls and generate house dust leading to ingestion by toddlers. For bio-persistent fat soluble insecticides, mother's milk may be an important source of exposure of newborns.

Dermal exposure, touching of contaminated surfaces (walls, floors, furniture). Potential residues on toddlers hands leading to hand-to-mouth ingestion exposure.

The target of the spraying is the wall surface. This is likely to lead to spray residues on the floor. It is recommended that floors are swept after the spray has dried in order to remove spray deposits from the floor to outside the house. The concentration of active ingredient close to the wall is similar to that of the wall and decreases progressively the further away from the wall until it is practically zero (Dr G. Matthews, personal communication, 2009). It is thus assumed that the average concentration in the 50-cm strip of the floor adjacent to the wall, represents 30% of that on the wall. In a

100 m² dwelling, the average concentration of the active ingredient on the floor would thus be 5.7% of the target concentration on the wall. The default concentration of the insecticide on surfaces with which inhabitants are in contact is 15% of the wall target concentration (10% of the contact with the walls, 90% with the floors and furniture)².

$$\text{Predicted dose} = \frac{0.15 \times AV \times TC \times Transl \times ESA \times AbsD}{\text{Body weight}}$$

Where:

- Predicted dose = systemic dose due to dermal exposure, mg a.i./kg BW per day
- *AV* = average proportion of spray residue on the wall during 6 months of first-order kinetics decay with a half time of 60 d (0.42).
- *TC* = target concentration on the wall, i.e., concentration of a.i. in the formulation mg/g × spray dilution g/mL × 40 mL/m²
- *Transl* = proportion translodged onto skin. The default used is 11% (95th percentile for hard surfaces (USEPA 2009).
- *ESA* = Exposed skin areas are 0.201 m² for adults (hands and forearms), 0.191 for 6-11-yr children (hands and arms) and 0.376 m² for toddlers (head, hands, arms, legs, feet (Table 3; USEPA, 2008). For toddlers, insecticide on the hands is partially transported to the mouth during hand-to-mouth activity and leads to ingestion exposure (see below).
- *AbsD* = dermal absorption, default 10%
- *BW* = body weight, 62 kg for adults, 32 kg for older children, and 14 kg for toddlers
- Exposure duration = averaging time, 365 days per year

Ingestion exposure

It is assumed that food items are removed before premises are treated and thus not directly sprayed. The default assumptions are that the amount available for transfer from contaminated shelf surfaces to food items is 11%; (US EPA 2009); the concentration of the active ingredient on the surfaces being 30% of the target concentration on the wall immediately after the spraying (shelf surface in the same position as floor within a 50-cm distance from the wall as far as the spraying is concerned), and decreasing exponentially with a T_{1/2} of 60 d, leading to an average concentration of 0.42 × the original concentration over the 6-month interval between sprayings. Half of the food is in contact with the shelf (the rest assumed to be either in bags or other wrappings, or peeled before use). Exposure is continuous.

$$\text{Predicted dose} = \frac{0.3 \times AV \times TC \times Transl \times 0.5 \times SAF \times AbsO}{\text{Body weight}}$$

² Floor concentration = 0.3 *T* × 0.5m × 38m/100m = 0.057 *T*; 10% contact with 100 *T*, 90% with 0.057 *T* = 0.15 *T*

Where:

- Predicted dose = systemic dose due to oral exposure, mg/kg BW per day
- *TC* = target concentration on the wall = concentration of a.i. in the formulation mg/g × spray dilution g/mL × 40 mL/m²
- *AV* = average proportion of spray residue on the wall during 6 months of first-order kinetics decay with a half time of 60 d (0.42)
- *Transl* = proportion translocated onto food; the default is 11% of the amount present on the surfaces are assumed to be translocable (USEPA 2009)
- *SAF* = surface area of food. The surface area of food (daily intake) is calculated from the daily weight of food eaten, 1100, 1100 and 1000 g/d for adults, children and toddlers (Table 3). The density of food is approx. 1 kg/dm³, and assuming that "food" is a cube, of which one surface, i.e., volume to the power ²/₃, is in contact with the shelf, *SAF* = 0.0107, 0.0107, and 0.01 m² for adults, children, and toddlers.
- *AbsO* = Absorption form the gastrointestinal tract. The default value is 100%
- Body weight = 62 kg for adults, 32 kg for older children and 14 kg for toddlers

Hand-to-mouth activity of the toddler

Insecticide is transferred to the hands from the surfaces contacted (see calculations above); the relevant hand area for toddlers is 0.032 m². For the extent of the transfer from hands to mouth, a default of 10% can be used. Therefore, the hand-to-mouth transfer of toddlers may be calculated from the dermal load estimated earlier in the document (dermal exposure via hands × 10%).

$$\text{Predicted dose} = \frac{0.15 \times AV \times TC \times Transl \times ESA \times THM \times AbsO}{\text{Body weight}}$$

Where:

- Predicted dose = systemic dose due to hand-to mouth transfer, mg a.i./kg BW per day
- *TC* = target concentration on the wall = Concentration of a.i. in the formulation mg/g × spray dilution g/mL × 40 mL/m²
- *AV* = average proportion of spray residue on the wall during 6 months of first-order kinetics decay with a half time of 60 d (0.42)
- *Transl* = proportion translocated onto skin: The default is 11% (USEPA 2009)
- *ESA* = exposed skin areas are 0.032 m²
- *THM* = transfer efficiency from the hands to the mouth, 10%
- *AbsO* = Absorption form the gastrointestinal tract. The default value is 100%
- *BW* = body weight, 14 kg

- Exposure duration = averaging time, 365 days per year

Hand-to-mouth behaviour and other activities carried out by toddlers may also cause ingestion of house dust. After IRS, the dust may be contaminated with the insecticide. Limited data indicate that the concentration of DDT in house dust is approximately 1 mg/kg after spraying, presumably at the WHO recommended dose rate of 2 g/m². The 95th percentile of dust eaten is 587 mg/d (USEPA, 1997); thus the daily dose of a 14 kg child would be 1 mg/kg × 587 mg/d / 14 kg bw = 0.042 µg/kg bw/d. As DDT because of its stability and high application rate probably represents the worst case, it seems that this pathway of exposure is generally, when other active ingredients are concerned, not toxicologically significant.

To estimate the maximal daily dose of the resident (for the assessment of acute toxicity by comparison to the TSD_{AC}), the total resident systemic dose is divided by 0.42 (thus using the target concentration on the wall instead of the average concentration).

Exposure via breast milk

Infant exposure from breast milk can be estimated from the equation:

$$\text{Predicted dose} = \frac{C \times IR \times A}{BW}$$

where

- Predicted dose = systemic dose from mother's milk, mg a.i./kg BW per day
- *IR* = ingestion rate of milk, kg/day, upper percentile default for a newborn is 950 mL/day (USEPA, 2008). If the density is assumed as 1 kg/L; the daily consumption would be 0.95 kg/day
- *A* = fraction absorbed, default being 100%
- *BW* = body weight, newborn, 4.8 kg (USEPA, 2008)
- *C* = concentration of the active ingredient in the breast milk is estimated from the exposure of the mother at steady state. Body burden = daily dose mg/kg bw × T_{1/2} (days)/ln2 (JECFA 2002). For water-soluble insecticides, the body burden is assumed to be concentrated in the water compartment of the body, and the concentration in breast milk equals this concentration; that is, the concentration in breast milk (mg/L) is 1.4 × body burden = 1.4 × daily dose mg/kg bw × T_{1/2} (days)/ln2. For lipid-soluble compounds (pK_{ow} ≥ 2), the insecticide is concentrated in the adipose tissue, and the concentration in adipose tissue is (20% fat content of the body) 5 × body burden mg/kg. The average fat content of breast milk is assumed to be 50 g/L, and the insecticide concentration in breast milk thus is:

$$C = \frac{D \times T_{1/2} \times 5 \times 0.05}{\ln 2} = 0.361 \times D \times T_{1/2}$$

- C = concentration of the insecticide in breast milk (mg/L)
- D = daily dose to the mother mg/kg bw
- $T_{1/2}$ = first-order kinetics half time in the body of the insecticide, days. Chemical-specific data to be used, as no meaningful default can be given.

Since this estimate is based on steady-state body burden of the mother, is also represents the maximal daily dose for the infant.

Chemical-specific data are likely to considerably increase the accuracy of this default value.

Reuse of contaminated pesticide product packages, acute ingestion exposure, adults and children

This clearly represents a gross misuse, which definitely should be outrooted, and need only be taken into account in specific situations. The exposure is acute.

$$\text{Predicted dose} = \frac{\text{FormC} \times \text{DF} \times \text{WIR} \times \text{AbsO}}{\text{BW}}$$

Where:

- FormC = concentration of the a.i. in the formulation; chemical specific data, mg a.i./L
- DF = dilution factor, approximately 1:20 volume by volume dilution, assumes 5% of insecticide residue in the emptied container, 0.05
- WIR = water ingestion rate, 2 L/day for adults, 1 L/day for children
- BW = body weight, 62 kg for adults, 32 kg for older children, and 14 kg for toddlers
- AbsO = Absorption from the gastrointestinal tract. The default value is 100%

Ingestion exposure from contaminated foodstuffs grown in an area contaminated from indoor residual spraying – adults, children and toddlers

Insecticide applied internally to the walls of houses and externally to house eaves will contaminate house dust, house floor materials and soil adjacent to the house at a low level; sweeping the house will transfer this contaminated material to the surrounding soil where vegetables and animals such as chickens might take up the insecticide. This could pose a significant route of human exposure if the insecticide is both persistent and bioaccumulative. If these properties apply, measurements should be made of actual levels in these media and food items.

4.2.3 Total exposure assessment

Total exposure is calculated by summing the contributions via different routes. The default absorption rates for ingestion, inhalation and dermal exposure are 100%, 100% and 10%, respectively. Any valid, chemical-specific data that are available should be used.

Exposure and risk should be calculated for operators and for residents (adults and children of different age groups) and for operators living in houses they have sprayed.

4.2.4 Uncertainties in exposure-determining factors and risk calculations

The default values for anthropometric measurements used in the risk assessment model are obtained from sources representing North American populations. Characteristics of African and Asian populations, for example, may be different. Generic datasets applicable to all populations, however, are not available.

Some defaults vary widely with the source of data. For example, estimates from agricultural exposure databases seem to give be higher than those from databases concerning residential exposure. For tasks such as mixing and loading, the agricultural databases are more suitable since the task is similar in agricultural and public health settings. For application tasks, however, the agricultural databases may not be the best possible source of data.

Dermal post-application exposure of residents of treated houses may occur for as long as the residues of the sprayed insecticide are found on treated surfaces. However, because of the diversity of surface materials used, persistence and decay of the active ingredients are difficult to estimate. Decomposition of active ingredients is a chemical feature for which data are often not available. This lack of information has traditionally caused problems also in assessing dermal exposure during re-entry activities in agricultural settings. Assessing one-day acute dermal exposure to liquid formulations is assumed to give a conservative estimate of exposure.

4.3 Risk characterization

The aim of the risk characterization is to evaluate the probability of adverse effects occurring under defined exposure conditions. In its simplest form, risk characterization consists of the comparison of estimates of exposure with TSDs defined in hazard assessment in all relevant exposure situations.

$$Ratio = \frac{\text{Estimated TWA systemic dose}}{TSD}$$

When this ratio is <1, the health risk is considered to be acceptable. When it is >1, there are possible health risks, and the planned use in indoor residual spraying may be unacceptable. In the cases of operators, however, it may be possible to reduce the risk – for example by changing recommended operational conditions or the amount of active ingredient in the technical product. A risk–benefit analysis, in which the risks of potential toxicity are compared with potential health benefits (disease prevention), may be needed in some cases.

When the insecticide has significant acute toxicity (e.g., JMPR or another organization has set an ARfD), the risk is also estimated for short-term exposure:

$$Ratio = \frac{\text{Estimated maximal daily systemic dose}}{TSD_{AC}}$$

In the publication *Generic risk assessment model for insecticide treatment and subsequent use of mosquito nets* (WHO, 2004), another approach to risk characterization, based on MOE (margin of exposure)[called MOS, margin of safety, in that document], is described. However, this alternative approach is not used to any significant extent in the context of public health pesticides and has therefore been omitted from the current document.

5. Conclusions

The models described in this document are intended for first-tier risk assessments; when better validated models are available, they should be used. The default values presented here are meant to serve as examples. Case-specific or substance-specific defaults or distributions for default parameters should be applied whenever available. In the interests of the transparency of the process, it is of utmost importance that the process is transparent and that the risk assessor can justify the decisions taken are soundly and scientifically justified and accurately recorded.

6. Summary of the human health risk assessment model and a worked example

In this worked example, a wettable powder formulation of insecticide "X" is used as a model compound.

Generic risk assessment model	Worked example
1. Toxicity data <i>Aim:</i> To assess available toxicity data and derive acceptable exposure levels.	1. Toxicity data <i>Aim:</i> To assess available toxicity data and derive acceptable exposure levels.
1.1 Conduct literature search for human, animal and in vitro toxicity data and any necessary physicochemical data on the insecticide.	1.1 Literature search on insecticide X conducted on MEDLINE, TOXLINE and sources of reviews (WHO/IPCS (EHCs, CICADs), JMPR, USEPA, PSD, IARC, ATSDR, etc).
1.2 Obtain relevant reviews and key original papers.	1.2 Comprehensive reviews available from WHO IPCS (EHC), USEPA, JMPR. Original key papers obtained.
1.3 Tabulate types of study, toxic effects observed, NOAELs and LOAELs.	1.3 All available relevant animal and human studies tabulated.
1.4 Assess whether quality of database is adequate for risk assessment (range of studies, conduct of studies, adequacy of dose–response data, etc).	1.4 Studies available on all relevant types of toxicity, mainly via oral route. No inhalation studies are available. One repeated dose dermal study in rabbits is available. Most studies are conducted to acceptable standards with adequate dose–response data.
1.5 If database is adequate, identify critical toxic effect(s).	1.5 Critical toxic effect in animal tests is neurotoxicity. In humans, skin symptoms such as burning and itching following contact have been described. More serious effects include dizziness, headache, nausea, paraesthesia and increased sweating. No dose response data are available on humans but database from animals is adequate.
1.6 If the insecticide is genotoxic, carcinogenic or extremely acutely toxic via dermal or oral routes, consider whether it is worth proceeding with risk assessment. Consider this also if it causes clear reproductive toxic effects at dose levels causing no general toxicity.	1.6 The substance is not genotoxic, carcinogenic or a specific reproductive toxicant. It has moderate acute oral toxicity in rodents and low acute toxicity dermally. Toxicity differs between different formulations. Toxicokinetic data suggest good oral absorption with usually >50% of the dose excreted in urine. Default 100% oral absorption is used in this assessment. Proceed with risk assessment.
1.7 If 1.6 does not apply, identify pivotal study/studies giving dose–response data for critical effect(s).	1.7 Pivotal studies were: <ul style="list-style-type: none"> • dog oral 1-year study, • dog oral 13-week study, • rat oral 13-week study, • rabbit dermal 3-week study

Generic risk assessment model	Worked example
<p>1.8 Identify critical NOAEL(s) from pivotal studies for acute exposure and for longer-term (repeat-dose) exposure.</p>	<p>1.8 Critical NOAELs:</p> <ul style="list-style-type: none"> dog oral 52-week study – NOAEL of 1.5 mg/kg bw and LOAEL of 3 mg/kg bw critical toxic effect being neurotoxicity rat oral 13-week study – NOAEL of 2.2 mg/kg bw with neurotoxicity at 6.7 mg/kg bw (LOAEL) rabbit dermal 3-week study – NOAEL 20 mg/kg bw per day for systemic effects, skin irritation observed also at 2 and 20 mg/kg bw
<p>1.9 Assess whether the database allows the setting of TSD.</p>	<p>1.9 Database is adequate for the setting of TSDs for long-term exposure. No data are available on inhalation exposure.</p>
<p>1.10 Set TSD by dividing NOAEL for the critical effect from the pivotal study via that route by an uncertainty factor (UF): $TSD = NOAEL/UF$ A default UF of 100 is recommended for NOAELs derived from animal studies. A default UF of 10 for NOAELs derived from human studies. (See main text for variations on these defaults.) Where other reputable bodies have set ADIs, RfDs, ARfDs, MRLs, etc use these to derive TSDs for IRS scenarios.</p>	<p>1.10 The ADI of 0–0.02 mg/kg bw per day is set by WHO. This is based on the 52-week dog study showing a NOAEL of 1.5 mg/kg bw per day and applying a UF of 100. Complete absorption from the gastrointestinal tract is assumed, meaning that the ADI of 0.02 mg/kg per day is considered to represent the total systemic dose TSD. In addition, WHO has set an ARfD of 0.04 mg/kg for insecticide X. The TSD_{AC} IS 0.04 mg/kg bw.</p>
<p>1.11 Conclusion on final TSD(s)</p>	<p>1.11 TSD used in risk characterization:</p> <ul style="list-style-type: none"> 0.02 mg/kg bw per day for total systemic exposure. $TSD_{AC} = 0.04$ mg/kg bw
<p>2. Exposure assessment The defaults and other data used in the assessments should not be limited to those presented in this document as examples. Searches should be made for case-specific, valid and scientifically sound data.</p> <p><i>Aim:</i></p> <ul style="list-style-type: none"> to estimate operator exposure via dermal, oral and inhalation routes during mixing and loading and when applying residual spray indoors, and during washing and maintenance of the spray equipment. to estimate residential exposure of adults, children and toddlers, i.e post-application acute dermal and ingestion exposure (to contaminated foodstuff); including the hand-to-mouth exposure of toddlers, and exposure of infants via breast milk. to estimate exposure of residents who also work as operators. 	<p>2. Exposure assessment In this worked example, a wettable powder formulation of a synthetic pyrethroid insecticide product "X" is assumed. The a.i. content of the formulation is 50 g/kg.</p> <p>A guideline scenario (label and WHO manual instructions are followed) and a lax standard scenario (which takes account, for example, of the effect of tropical weather conditions on the use of PPE) are presented.</p>

Generic risk assessment model	Worked example
<p>2.1 Operator exposure during mixing and loading, application and washing and maintenance of the equipment</p> <p>During mixing and loading, inhalation exposure is negligible</p> <p><i>a) Dermal exposure during mixing and loading</i></p> <p>Dermal exposure during mixing/loading is estimated by using unit exposures from a database. In lax standard scenario, it is assumed that there is no use of PPE (gloves); in guideline scenario estimations, gloves are used.</p>	<p>2.1 Operator exposure during mixing and loading, application and washing and maintenance of the equipment</p> <p><i>a) Dermal exposure during mixing and loading</i></p> <p>The target concentration on the wall is 32 mg/m². The concentration needed for the spray liquid is 32 /40 = 0.8 mg/mL. Therefore, 8000 mg of insecticide, suspended in 10 L of water (one tank), gives a concentration of 0.8 mg/mL. As 12 tank loads are prepared and used daily, the amount of insecticide a.i. handled is 12 x 8000 mg = 96 000 mg = 0.096 kg per day.</p> <p>Dermal exposure is 9.7 mg a.i./kg a.i. (default for a WP), i.e., = 9.7 x 0.096 = 0.93 mg/day.</p> <p>The dermal absorption is 10%, exposure time and the averaging time, 72 days and 365 days; body weight 60 kg. In the lax standard scenario, the systemic exposure during mixing and loading (no PPE) is $0.1 \times 0.93 \times 72 / (365 \times 62) = \mathbf{0.30 \mu g/kg \text{ bw/d}}$ In the guideline scenario, the PPE is assumed to provide 90% protection, and the predicted dose is 0.03 $\mu g/kg \text{ bw/d}$.</p>
<p><i>b) Inhalation exposure during application</i></p> <p>The default room size is 10 x 10 x 2 m³, the wall surface thus 80m², and volume 200 m³. The proportion of the spray released and distributed evenly in the room air is 0.1%. In the guideline scenario, PPE provides a 90% protection Breathing rate is 1.9 m³/h, exposure time, 4h/d. Respiratory absorption is 100%. The exposure time is 72 d and the averaging time 365 days Body weight of an adult operator is 62 kg.</p>	<p><i>b) Inhalation exposure during application</i></p> <p>The sprayed amount of the a.i. 80 m² x 32 mg/m² = 2560 mg. The concentration of the insecticide in the inhaled air, is 0.001 x 2560/200 = 0.013 mg/m³. The amount inhaled is 0.013 x 1.9 x 4 = 0.097 mg The inhaled dose during application in the lax-standard scenario = 0.31 $\mu g/kg \text{ bw/d}$, in the guideline scenario = 0.03 $\mu g/kg \text{ bw/d}$</p>
<p><i>c) Dermal exposure during application and washing and maintenance of the equipment</i></p> <p>It is assumed that during the working day, the surface of the hands is contaminated with the spray liquid. In the guideline scenario, gloves are assumed to give 90% protection. The liquid layer covering the hands is assumed 9.3 mL</p>	<p><i>c) Dermal exposure during application and washing and maintenance of the equipment.</i></p> <p>The concentration of the a.i. in the spray is 0.8 mg/mL. Therefore, the exposure via hands (no PPE) is 7.44 mg a.i./day. When the dermal absorption of 10%, exposure duration (72 days/year), the averaging time (365 days/year), and the body weight (62 kg) are taken into account, predicted systemic dose from dermal exposure in the lax standard scenario is 2.4 $\mu g/kg \text{ bw/d}$. In the guideline scenario, the gloves give 90% protection, the predicted dose is 0.24 $\mu g/kg \text{ bw/d}$.</p>

Generic risk assessment model	Worked example
<p><i>d) Total TWA operator predicted dose</i> Dermal and inhalation exposure in mixing, loading, spraying, and washing and maintenance of the equipment added together</p>	<p><i>d) Total TWA operator predicted dose</i></p> <p>Guideline scenario: $\text{Dose}_{\text{M/L Dermal}} + \text{Dose}_{\text{A Inhalation}} + \text{Dose}_{\text{A Dermal}} = 0.03 + 0.03 + 0.24 = 0.3 \mu\text{g} / \text{kg bw}.$</p> <p>Lax standard scenario: $\text{Dose}_{\text{M/L Dermal}} + \text{Dose}_{\text{A Inhalation}} + \text{Dose}_{\text{A Dermal}} = 0.30 + 0.31 + 2.4 \mu\text{g} = 3.0 \mu\text{g} / \text{kg bw}$</p> <p>The maximal systemic daily dose in the guideline scenario is 1.5 $\mu\text{g}/\text{kg bw}$ and 15 $\mu\text{g}/\text{kg bw}$ in the lax standard scenario</p>
<p>2.2 Residential dermal exposure due to touching contaminated surfaces, adults, children, toddlers</p> <p>The residue on the floor surfaces of a treated dwelling of 100 m² is assumed to be 5.7% of the target concentration on the walls, on average. The default average concentration of the insecticide on the surfaces that the residents are in contact with is 15% of the wall target concentration.</p> <p>The default T_{1/2} if the insecticide on the surface is 60d, and thus the average concentration over the 60-d spraying interval is 0.42 × the initial concentration.</p> <p>Amount translocable onto skin is 11% of the amount present on the surfaces.</p> <p>Default skin areas exposed: 0.201 m² for adults (hands and forearms) 0.191 for children (hands and arms) 0.376 m² for toddlers (head, hands, arms, legs, feet)</p> <p>The hand area relevant for the hand-to-mouth exposure for toddlers is 0.032 m².</p> <p>For the transfer from hands to mouth, a default of 10% can be used.</p> <p>Dermal absorption is assumed to be 10%, if no other (chemical specific) data can be found.</p> <p>Body weight, 62 kg for adults, 32 kg for older children, and 14 kg for toddlers.</p> <p>Exposure is assumed continuous; that is, exposure duration = averaging time.</p>	<p>2.2 Residential dermal exposure due to touching contaminated surfaces, adults, children, toddlers</p> <p>The target concentration of the a.i. on the walls is 32 mg/m².</p> <p>The average concentration of the a.i. on the contact surfaces is 4.8 mg/ m² immediately after the spraying, and during the 6 months on an average, 0.42×4.8 = 2.0 mg/ m²; The average translocable proportion is 11% of this, 0.22 mg/ m².</p> <p>Predicted doses:</p> <ul style="list-style-type: none"> Adults: $0.22 \text{ mg}/\text{m}^2 \times 0.201 \text{ m}^2 \times 0.1 / 62 \text{ kg} = 0.07 \mu\text{g} / \text{kg bw}$ Children: $0.22 \text{ mg}/\text{m}^2 \times 0.191 \text{ m}^2 \times 0.1 / 32 \text{ kg} = 0.13 \mu\text{g} / \text{kg bw}$ Toddlers, dermal: $0.22 \text{ mg}/\text{m}^2 \times 0.376 \text{ m}^2 \times 0.1 / 14 \text{ kg} = 0.60 \mu\text{g} / \text{kg bw}$ Toddlers, potential hand-to-mouth: $0.22 \text{ mg a.i.}/\text{m}^2 \times 0.032 \text{ m}^2 = 7.0 \mu\text{g}/\text{hands}$ (to be calculated further, see 2.4).

Generic risk assessment model	Worked example
<p>2.3 Residential ingestion exposure due to contaminated foodstuff, breast milk or hand-to-mouth behaviour</p> <p><i>2.3.1 Contaminated foodstuff</i></p> <p>Adults weigh 62 kg, older children 32 kg, and toddlers (who also get ingestion exposure due to hand-to-mouth behaviour) 14 kg. Newborn babies consuming only breast milk are assumed to weigh 4.8 kg.</p> <p>The amount available for transfer from contaminated surfaces, i.e., kitchen furniture, is 11% of the a.i. on the contact surfaces, which are assumed to be covered with 30% of the target concentration of the treated walls. The concentration decreases with a $T_{1/2}$ of 60 days. The average concentration, therefore, is $0.42 \times$ the original concentration over the 1/2 -year interval between sprayings.</p> <p>The daily food consumption rate for adults, children and toddlers is 1100, 1100 and 1000 g, the contaminated surface thus 0.0107, 0.0107 and 0.01 m^2, respectively. Half of the food is in contact with the contaminated surfaces</p>	<p>2.3 Residential ingestion exposure due to contaminated foodstuff, breast milk or hand-to-mouth behaviour</p> <p><i>2.3.1 Contaminated foodstuff</i></p> <p>The target concentration on the walls is 32 mg/m^2. The average translocable part over the 6 month period between sprayings is $0.3 \times 0.42 \times 32 \times 0.11 = 0.44 \text{ mg a.i./m}^2$. Gastrointestinal absorption of 100% is assumed.</p> <p>Predicted average daily dose over the 1/2-year time period of one spraying from consumption of contaminated food for 62 kg adult: $0.5 \times 0.44 \times 0.0107 / 62 \text{ kg} = \mathbf{0.04 \mu\text{g/kg bw}}$</p> <p>Predicted dose due to consumption of contaminated food for a child (32 kg) $0.5 \times 0.44 \times 0.0107 / 32 \text{ kg} = \mathbf{0.07 \mu\text{g/kg bw}}$</p> <p>Predicted systemic dose for a toddler (14 kg): $0.5 \times 0.44 \times 0.01 / 14 \text{ kg} = \mathbf{0.16 \mu\text{g/kg bw.}}$</p>
<p>2.4 Residential ingestion exposure of toddlers via hand-to-mouth behaviour</p> <p>It is assumed, that the hand-to-mouth behaviour is only common for toddlers, i.e. 14 kg can be used as a default body weight.</p> <p>10 % transfer from hands to mouth is applied as a default. Gastrointestinal absorption of 100% is assumed.</p>	<p>2.4 Residential ingestion exposure of toddlers via hand-to-mouth behaviour</p> <p>Note: See post-application dermal exposure calculation for the estimation of the amount of insecticide residue in toddler's hands.</p> <p>Predicted dose due to toddlers' hand-to-mouth behaviour: $0.22 \text{ mg/m}^2 \times 0.032 \text{ m}^2$ $= 7.0 \mu\text{g a.i./hands} \times 10\% / 14 \text{ kg}$ $= \mathbf{0.05 \mu\text{g/kg bw}}$</p>

Generic risk assessment model	Worked example
<p>2.4.1 Residential ingestion exposure via breast milk</p> <p>The breast milk exposure calculation presented here is a very rough estimation. Use of chemical-specific data is highly recommended.</p> <p>Default absorbed fraction is 100%.</p> <p>Concentration in the breast milk is calculated using the exposure of the mother at steady state as a starting point. Body burden = daily systemic dose mg a.i./day $\times T_{1/2}$ (days)/ln2.</p> <p>Insecticide X is lipid-soluble. For lipid solubles ($pK_{ow} \geq 2$), the concentration in breast milk mg/kg milk fat = $5 \times$ body burden (assuming 20% fat content of the body). Average fat content of breast milk is assumed to be 50 g/L. The concentration in breast milk for a lipid soluble insecticide thus = systemic dose mg a.i./kg bw $\times 5 \times 0.05$ kg/L $\times T_{1/2} / \ln 2$.</p> <p>Ingestion rate for new born = 950 mL/day = 0.95 kg/day (density 1 kg/L)</p>	<p>2.4.1 Residential ingestion exposure via breast milk</p> <p>For the insecticide X, $T_{1/2} = 1$ d; gastrointestinal absorption = 100% For the newborn child of a mother who is resident of a treated dwelling the predicted doses are: $100\% \times 0.11 \mu\text{g /kg bw} \times 5 \times (1.0/0.693) \times 0.05 \times 0.95 \text{ kg/day} / 4.8 \text{ kg}$ = 0.008 $\mu\text{g / kg bw/day}$. For a mother also works as a spray operator</p> <p>Guideline operator scenario: $100\% \times 0.41 \mu\text{g /kg bw} \times 5 \times (1.0/0.693) \times 0.05 \times 0.95 \text{ kg/day} / 4.8 \text{ kg}$ = 0.029 $\mu\text{g a.i./kg bw/day}$.</p> <p>Lax standard scenario: $100\% \times 3.09 \mu\text{g /kg bw} \times 5 \times (1.0/0.693) \times 0.05 \times 0.95 \text{ kg/day} / 4.8 \text{ kg}$ = 0.22 $\mu\text{g /kg bw/day}$.</p> <p>These estimates of TWA exposure also represent maximal daily dose, as it is based on the steady-state body burden of the mother.</p>
<p>2.5 Reuse of contaminated pesticide product packages</p> <p>This represents a gross misuse, which definitely should be outrooted, and need only be taken into account in specific situations.</p>	<p>2.5 Reuse of contaminated pesticide product packages</p> <p>A solid formulation is used. Therefore, reusing the packages is not considered a relevant cause of exposure.</p>
<p>2.6 Residents participating in insecticide preparation and application</p> <p>Exposure of the residents who also apply the insecticide is calculated by summing up the predicted doses for operators (mixing and loading + application, washing and maintenance) and adult residents (eating contaminated foodstuff + touching contaminated surfaces). It is assumed that only adults work as insecticide operators.</p>	<p>2.6 Residents participating in insecticide preparation and application</p> <p>The predicted dose for a resident working as spray operator in guideline scenario:</p> <p>Total predicted dose of operator + Total predicted dose of adult resident = 0.4 $\mu\text{g/kg bw}$.</p> <p>The predicted dose in lax standard for a resident working as spray operator:</p> <p>Total predicted dose of operator + Total predicted dose of adult resident = 3.1 $\mu\text{g/kg bw}$.</p>

Generic risk assessment model	Worked example
<p>3. Risk characterization</p> <p>3.1 Comparison of exposure estimates with TSDs for operator risk characterization</p> <p>For products with appreciable acute toxicity or irritative properties, consideration should be given to acute reference doses.</p> <p>If the exposure calculated for a sub group and exposure route is below the respective limit value, in worst case conditions, it can be assumed that the exposure is acceptable, and it does not cause unacceptable risk to human health.</p> <p>If the exposure is above the TSD and refining the assessment process e.g. by the use of chemical-specific data fails to bring the exposure below the TSD, measures to reduce the exposure have to be implemented</p> <p>In some cases the exposure is found unacceptable. Other methods of vector control should be considered.</p>	<p>3. Risk characterization</p> <p>3.1 Comparison of exposure estimates with TSDs for operator risk characterization</p> <p>The irritation capacity and acute toxicity of X are low. Thus local effects and acute toxicity are not important aspects in the risk assessment, which is based on comparison with the long-term toxicity and the long-term TSD.</p> <p>From 1.11 TSD used in subsequent risk characterization is 0.02 mg/kg bw per day, and TSD_{AC} = 0.04 mg/kg bw</p> <p>Predicted doses to be used in subsequent risk characterization:</p> <p><i>Total TWA operator predicted doses:</i></p> <p>Guideline scenario: Dose_{ML} Inhalation + Dose_{M/L} Dermal + Dose_A Inhalation + Dose_A Dermal = 0.3 µg/kg bw/d.</p> <p>Lax standard scenario: : Dose_{ML} Inhalation + Dose_{M/L} Dermal + Dose_A Inhalation + Dose_A Dermal = 3.0 µg/kg bw/d</p> <p>In the guideline and lax standard scenarios, operator exposure is acceptable, 1 and 15% of the TSD.</p> <p>Total maximal operator systemic dose in guideline scenario is 1.5 µg/kg bw and in lax standard scenario 15 µg/kg bw.</p> <p>The maximal systemic dose of the operator is acceptable in the guideline scenario (4% of TSD_{AC}) and also in the lax standard scenario (40% of TSD_{AC})</p> <p><i>Total resident predictedTWA systemic doses:</i></p> <p>Adults Dose from touching contaminated surfaces + Dose from eating contaminated foodstuff = 0.1 µg/kg bw Adult resident exposure is considered acceptable. The predicted dose is 0.6% of the TSD.</p> <p>Children Dose from touching contaminated surfaces + Dose from eating contaminated foodstuff</p>

Generic risk assessment model	Worked example
	<p>= 0.2 µg/kg bw Resident child exposure is considered acceptable. The predicted dose is 1% of the TSD.</p> <p style="text-align: center;">Toddlers</p> <p>Dose from touching contaminated surfaces + Dose from eating contaminated foodstuff + Dose from hand-to-mouth behaviour = 0.8 µg/kg bw Resident toddler exposure is considered acceptable. The predicted dose is 4% of the TSD.</p> <p style="text-align: center;">New born babies – breast milk exposure</p> <p>In the lax standard scenario, operator + residential exposure, the predicted systemic exposure of the newborn = 0.22 µg/kg bw/day</p> <p>Exposure of new born babies is considered acceptable. The predicted dose is 1.1% of the TSD.</p> <p>The maximal daily dose of residents is acceptable, 1, 2, 8, and 1% of the TSD_{AC} for adults, children, toddlers, and infants, respectively.</p> <p style="text-align: center;">Residents who also work as spray operators</p> <p>Predicted dose in guideline scenario = 0.4 µg/kg bw. Predicted dose in lax standard scenario = 3.1 µg/kg bw. Exposure of residents working as spray operators in the guideline and lax standard scenarios is considered acceptable. The predicted exposure is 2% and 15% of the TSD, respectively.</p>

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