GENERIC RISK ASSESSMENT MODEL FOR INDOOR RESIDUAL SPRAYING OF INSECTICIDES

SECOND EDITION

World Health Organization

Generic risk assessment model for indoor residual spraying of insecticides

2nd Edition

World Health Organization
Communicable Diseases cluster
Department of Control of Neglected Tropical Diseases
Vector Ecology and Management
&
Climate and Other Determinants of Health cluster
Department of Public Health, Environmental and Social Determinants of Health
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The Secretariat revised the document based on these comments; advice was then sought on open questions in an expert consultation from Health Canada of the Government of Canada, the British Health and Safety Executive, the Finnish Institute of Occupational Health and the Dutch National Institute for Public Health and the Environment (RIVM). The document was then finalized by the Secretariat as the second edition. Comments received during peer review and the views of experts consulted during the expert consultation were advisory in nature, and the contents of the document are the responsibility of the Secretariat.

Terminology, abbreviations and acronyms

ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
ATSDR	United States Agency for Toxic Substances and Disease Registry
AUC	area under curve
BCF	bioconcentration factor
BMD	benchmark dose
CICAD	Concise International Chemical Assessment Document
EC	European Commission
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
EU	European Union
EUROPOEM	European Predictive Operator Exposure Model
GHS	Globally Harmonized System of Classification and Labelling of Chemicals (United Nations, 2015)
GLP	good laboratory practice
guideline scenario	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
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPM	Joint FAO/WHO Meeting on Pesticide Management
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
lax standard scenario	no personal protective equipment other than light clothing covering the trunk is assumed
LOAEL	lowest-observed-adverse-effect-level
MRL	minimal risk level
NOAEL	no-observed-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
POEM	Predictive Operator Exposure Model
PPE	personal protective equipment
PSD	Pesticides Safety Directorate of the United Kingdom Health and Safety Executive
RfC	reference concentration
RfD	reference dose
RPE	respiratory protective equipment
TSD	tolerable systemic dose
TSDAC	Tolerable systemic dose, acute exposure
TWA	time-weighted average
UF	uncertainty factor
UKPOEM	UK Predictive Operator Exposure Model
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme

1. Introduction

Indoor residual spraying (IRS) 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, Chagas disease and visceral leishmaniasis.

The equipment used for indoor residual spraying is typically a hand compression sprayer fitted with a fan-type nozzle and a control flow valve. The World Health Organization (WHO) has published specification guidelines on equipment for vector control (WHO, 2010). Procedures for indoor residual spraying are described in a separate manual (WHO, 2007).

The formulations commonly used for indoor residual application of insecticides are wettable powders, suspension concentrates, capsule suspensions and water-dispersible granules. Wettable powders or water dispersible granules in sealed water soluble bags are also formulated and provide ease of handling and mixing in a spray tank and reduce spray operators' risk (WHO, 2007). Emulsifiable concentrates are generally not suitable for use in indoor residual spraying.

The requirements, procedures and criteria for testing and evaluation of insecticides for IRS for control of malaria and Chagas disease vectors are available from WHO (http://www.who.int/whopes/guidelines/en/).

2. Purpose

This document provides a generic model that can be used for the 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; and
- residents who participate in preparing and applying insecticides.

The structure of this document follows that of *A generic risk assessment model for insecticide treated nets* (WHO, 2018). 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.

The WHO recommended insecticides for indoor residual spraying are listed on the WHO website (http://www.who.int/whopes/en/).

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 point estimate of the exposure is compared with a health-based guidance value, which is also a point estimate. For the screening – or first-tier assessment – of products, the deterministic assessment is completely appropriate. However, it has an important drawback in that it incorporates no information about the variability of exposure.

The probabilistic technique offers a complementary modelling approach that incorporates variability of exposure between individuals and at different points in time and allows an assessment of the uncertainty of the assessment outcome (uncertainty of data, such as limited availability of empirical information, as well as limitations in the measurements, models or techniques used to develop representations of complex physical, chemical and biological processes) (WHO, 2008). Probabilistic modelling uses distributions of values rather than single values. The advantage of the technique is that it provides the probability of occurrence and/or amount of exposure, which offers a realistic and informative way of characterizing 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, or USEPA). 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 are easier to understand and more "user-friendly" are under development and should be available 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 has proved to be a very useful technique in more complex situations or when deterministic assessments have identified exposures of concern (second- and 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 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; WHO, 2009b); 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*. Consideration of any *uncertainties* in the hazard assessment, exposure assessment and risk characterization 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, as well as 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 insecticide 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 reality that 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 sections of this document 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 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
- 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; WHO, 2009b); they are generally applicable to all chemical classes and patterns of use, although there may be some differences, e.g. in data requirements.

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 data (in vivo and in vitro) and human data. It is recommended that, when available, risk assessments that have already been generated for 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 type of authoritative evaluation are given in Table 1. Many can be accessed on the Internet, for example via OECD's eChemPortal (http://www.echemportal.org)

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
If insecticides 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 insecticide formulations in question, or general population studies; and
- ethically approved volunteer studies examining mild, temporary effects of acute 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.who.int/ipcs/publications/cicad/en/
Environmental Health Criteria Monographs	http://www.who.int/ipcs/publications/ehc/en/
International Agency for Research on Cancer (IARC) – Monographs on the Evaluation of Carcinogenic Risks to Humans	http://monographs.iarc.fr/ENG/Monographs/PDFs/
United States Environmental Protection Agency (USEPA) – Pesticide evaluations	https://iaspub.epa.gov/apex/pesticides/f?p=chemic
European Food Safety Authority (EFSA) – Pesticide Risk Assessments	http://www.efsa.europa.eu/en/pesticides/pesticide
European Chemicals Agency – Information on Chemicals search page	https://echa.europa.eu/information-on-chem

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 (2011) or USEPA (2010). For older insecticides, 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 insecticides).

Like all substances, public health insecticides 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 insecticide, 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 technical materials of the active ingredients or solvents used in insecticide formulations rather than for the formulations themselves. Sometimes, however, some acute toxicity tests may also be performed with an insecticide formulation.

4.1.3 Range of toxicity tests normally required for pesticide approval

In addition to the general requirements outlined in the previous section, 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 operators and of inhabitants of treated areas. Inhalation toxicity studies may also 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.

- **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. There may be occasions where in vitro tests may replace the need for the whole animal tests described above.

Absorption of the insecticide by inhalation, 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 are used. For dermal absorption of insecticides with molecular mass > 500 and octanol/water partition coefficient (log P_{OW}) < −1 or > 4, 10% is used as the default. Since dermal absorption of several pyrethrins and pyrethroids has been shown to be in the order of 1%, it is reasonable to apply a default dermal absorption value of 10% rather than 100% for pyrethrins and pyrethroids when chemical-specific data are not available. However, it must be emphasized that if the assessor is aware that specific data exist for a pyrethroid, those data should be used in preference to the default value. A similar bridging approach could be developed for other chemical groups of pesticides. For insecticides other than pyrethroids when no data are available, the concept of an inverse relationship between concentration and dermal absorption is applied: for pesticide formulations with the active ingredient (a.i.) content > 5%, a default dermal absorption value of 25% is used, while for mixtures with a concentration ≤ 5%, the default used is 75% (EFSA, 2012). In the absence of good-quality data on dermal absorption of dry insecticides deposited on the skin or transferred from surfaces, the higher estimate (concentrated or dilute) of the active ingredient is used (EFSA, 2011, 2014). 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. 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 (EFSA, 2012).

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 of classification and labelling of chemicals* or GHS (UN, 2015) 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.

The recent International Code of Conduct on Pesticide Management (FAO/WHO, 2014) also states that prohibition of the importation, distribution, sale and purchase of highly hazardous pesticides may be considered if, based on risk assessment, risk

mitigation measures or good marketing practices are insufficient to ensure that the product can be handled without unacceptable risk to humans and the environment. It is suggested that this recommendation be followed in the case of products for 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 as the basis for risk characterization.

4.1.6 Mixtures of insecticides and insecticides with other constituents of the formulation

If two or more insecticides are used concurrently, possible interactions between those insecticides should be considered. Insecticides with similar action may produce additive toxic effects (dose/concentration addition); organophosphates, for example, decrease acetylcholinesterase activity. For toxicants with dissimilar (independent) action, the combined effect can be estimated directly from the probability of responses to the individual components (response addition) or the sum of biological effects (effects addition). Other forms of interaction include synergistic (supra-additive) or antagonistic effects, which may be caused by different classes of insecticides, for example because of metabolic interactions. Synergism is usually only noted at high exposure levels, and may be considered unlikely at levels acceptable for the individual components (SCHER, 2011). In this document, the conservative recommendation of IPCS to consider effects of mixtures as dose/concentration additive (Meek et al., 2011) is adopted as the default, except in cases in which a different mode of action has been demonstrated for the two components of the mixture.

Interactions may also occur between the active ingredient and the solvent(s) used in the formulated product. Moreover, impurities, 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 dose 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 endocrine-mediated toxicity, however, the shape of the dose–response curve may not be well defined, which poses problems for the risk assessment of substances with such activity.

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, a NOAEL and/or LOAEL can be identified. For genotoxicity and carcinogenicity mediated by genotoxic mechanisms, dose–response is considered linear, meaning that risk cannot be excluded at any exposure level. For non-genotoxic carcinogenicity mechanisms, the critical cancer events may be threshold phenomena.

The NOAEL and LOAEL values are study-specific dose levels at which no adverse effects or minimal adverse 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 the critical effects may not always be the same for each exposure scenario. For example, for scenarios involving high-level acute exposure to an acutely toxic insecticide, such as spraying of the insecticide, acute effects and irritation may be identified as critical effects, whereas effects from long-term/chronic studies should be considered in setting of reference values for long-term low-level residual exposure of inhabitants of treated buildings via skin and hand–mouth contact.

The following additional points should be noted when identifying NOAELs/LOAELs for insecticides (WHO, 2009a):

- 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, 2009a). Whereas a NOAEL represents a dose level assumed to be without appreciable effect, a BMD 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 an NOAEL is used by applying similar uncertainty factors. 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 assumed 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, 2009a).

Setting tolerable systemic doses: the use of uncertainty factors

In the setting of tolerable systemic dose levels (TSDs), critical NOAELs/LOAELs (or BMDs), (corrected for absorption) are divided by uncertainty factors (UFs) to account for variability and uncertainties. Thus a TSD can be derived from long-term studies on oral toxicity:

$$TSD = Abs_{oral} \times N(L)OAEL/UF$$

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 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 x 10 = 100 (WHO, 1994; WHO, 1999). However, this default approach can be modified if appropriate chemical-specific toxicokinetic or toxicodynamic data exist that justify smaller or larger 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 (WHO, 2005a, Bhat et al., 2017).

The default setting of a TSD is based on cumulative effect upon repeated/continuous exposure. Thus the systemic dose is averaged over a year, and years are thought be similar vis à vis exposure. Furthermore, the effect is considered to be linked to the total absorbed dose, which is reflected in the plasma area under curve (AUC) – from which the kinetic variability factors $10^{0.6} = 4$ for interspecies uncertainty, and $10^{0.5} = 3.16$ for human interindividual variability are derived. However, this is not necessarily true for all insecticides. For example, some carbamates are rapidly excreted, and they exert their toxic effect through transient, reversible inhibition of cholinesterase enzyme. The rapid reactivation of carbamate-inhibited enzyme means that the toxic effect mainly depends on the peak plasma concentration (C_{max}) and is not cumulative. Since the C_{max} varies less than the area under the plasma concentration curve (AUC), the kinetic component of interspecies extrapolation and

the kinetic component of the interindividual human differences may both be lowered 50% [2 and 1.58, respectively], and the overall variability factor thus be lowered from the traditional 100 (4×2.5×3.16×3.16) to 25 (2×2.5×1.58×3.16) (JMPR, 2008). When the effect is not cumulative over time as is the case for some carbamates, as substantiated by data on bendiocarb (JMPR, 1982, 1984), the dose averaging over time is not appropriate; rather, the maximal daily dose is compared with the ADI.

In some cases, the use of additional UFs is justified (Dorne and Renwick, 2005; Dourson, Knauf & Swartout, 1992; Herrman & Younes, 1999; Vermeire et al., 1999; 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 (e.g. 3–10) 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).
- The effect is not cumulative and is related to peak plasma concentration, not AUC (see above).

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, however, it is also important to verify that the maximal daily exposure is acceptable; for this purpose, the tolerable systemic dose for acute exposure, TSD_{AC} (based on, for example, the acute reference dose, 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 per body weight per day (mg $kg_{bw}^{-1}d^{-1}$). 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 (EU), and reference doses or concentrations (RfDs, RfCs) set by the USEPA. 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 dietary 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 Joint FAO/WHO Expert Committee on Food Additives (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. However, 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 absorption via the skin which, for exposure to insecticides, may be more significant than that via inhalation. 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 indoor residual spraying guidelines thus usually need to be significantly larger than those applied in setting OELs.

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

Acute exposure

Guidance values for acute (24-hour) dietary exposure to agricultural plant protection products has been set by JMPR 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 (ARfDs).

The 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, 1998b; Solecki et al., 2005). It is derived similarly to the long-term ADI, using relevant human or animal studies of acute 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 different UF (see above).

For organophosphates and carbamates, inhibition of acetylcholinesterase in either red blood cells or brain, measured minutes to hours after dosing (and compared with a value before exposure), is an appropriate parameter on which to base the guidance value for acute exposure. For example, the ARfD for chlorpyrifos is based on a study in human volunteers, in which an NOAEL 1 mg kg_{bw}^{-1} was identified for the inhibition of erythrocyte acetylcholinesterase activity (JMPR, 1999). As the study was 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 into account the acute risks related to, for example, insecticide application, spillages and oral exposure of residents from use of insecticide containers for storing drinking-water.

For most of the common insecticides used for indoor residual spraying, 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, 2012). 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 indoor residual spraying when no authoritative acute reference dose is available.

4.2 Exposure assessment

The second step in performing a risk assessment is to estimate exposure to the insecticide in the various groups of people potentially at risk. Exposure must take account of various parameters, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality, and whether this exposure is intermittent or continuous. The following groups of people may be exposed to insecticide through indoor residual spraying:

- spray operators
- residents
  - adults
  - children (including breastfed infants).

Exposure algorithms, default values and unit exposures, which describe the relationship between operational conditions and exposure, are taken from *Standard operating procedures for residential pesticide exposure assessments* (USEPA, 2012), and *Exposure factors handbook: 2011 edition* (USEPA, 2011); different agricultural field-study databases and modelling approaches (European Predictive Operator Exposure Model (EUROPOEM, 2003); and the 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 yield more accurate exposure predictions.

The ability of an insecticide 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 is also 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 systemic dose 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. Guidance on exposure models and communicating uncertainties has been published by WHO (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, perspiration on 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 to spray operators and residents in sprayed houses (adults and children) in:

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

Excessively high exposures from malfunctioning equipment and clear misuses are not covered in this risk assessment.

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.

- Risks for residents are estimated for adults, children (aged 6–11 years), toddlers (aged 12–24 months) and infants (aged < 12 months), as recommended by the European Human Exposure Expert Group (HEEG, 2013a). Exposure via mother's milk is estimated for infants and newborns (birth to 1 month).
- Anthropometric and physiological input parameters (weight, skin surface area and ventilation rate) have an effect on the risk estimates. Ideally, data from the target population should be used. However, it is also important that the database is internally consistent: all needed parameters for all age groups are available and are derived from the same population. The database produced by the USEPA (2011) is extensive and up-to-date, covering all age groups and all relevant anthropometric and physiological data-points. It is also recommended for use by the European Human Exposure Expert Group (HEEG, 2013a), and was therefore used in this document (Table 3). For body weight, the 25th percentiles are applied; for respiration rate, the HEEG recommendations are used. When appropriate anthropometric data are available for the population for which the risk assessment is made, these should be used.
- Adult spray operators and residents are assumed to weigh 60 kg. Risks are also estimated for children aged 6–11 years (assumed to weigh 23.9 kg), toddlers aged 12–24 months (10 kg) and infants from birth to 12 months of age (8 kg). Exposure via mother's milk is assessed also for newborns (birth to 1 month, weight 4.2 kg (USEPA, 2011; HEEG 2013a).
- 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 8.2 mL is the maximum amount of liquid on the hands of an adult (total surface area of hands 820 cm^2; for children this volume is 4.3 ml (see Table 3) (USEPA, 2011; HEEG 2013a).
- In most instances, exposure assessment consists of multiplication of several estimated parameters with an inherent variability (e.g. transfer from wall to hand skin, fraction of hand surface area mouthed, salivary extraction rate). If for each such parameter a high percentile of the distribution, say 95th percentile is used, this leads to an exposure estimate that is unrealistically conservative. Therefore, when available, a lower percentile is applied, usually the 75th percentile.

Table 3. Anthropometric and physiological characteristics used in the model (USEPA, 2011**;** HEEG, 2013a**)**

	Adult	**Child 6–11 yr**	**Toddler 12–24 mo**	**Infant ≤ 12 mo**
Weight[a] (kg)	60	23.9	10	8
Body surface[a] (m^2)				
total	1.6600	0.9200	0.4800	0.4100
hands	0.0820	0.0428	0.0230	0.0197
arms	0.2270	0.1270	0.0619	0.0582
forearms	0.1129	0.0497	0.0269	0.0230
legs	0.5330	0.2742	0.1219	0.1041
lower legs	0.230[c]	0.1070[d]	0.054[e]	0.046[e]
feet	0.1130	0.0605	0.0288	0.0246
head	0.1110	0.0529	0.0403	0.0344
trunk	0.5710	0.3376	0.1795	0.1533
Respiration rate[b]				
short-term (m^3/hour)	1.25	1.32	1.26	0.84
long-term (m^3/24-hour day)	16	12	8	5.4

[a] Weight and body surface are 25th percentiles based on females (aged 30–40 years, 6–11 years, 12–24 months, and 6–12 months (representing infants ≤ 12 months)) (USEPA, 2011, as recommended by HEEG, 2013a).
[b] These values represent mean values under moderate physical workload (USEPA, 2011; HEEG, 2013a).
[c] Source: USEPA, 2011.
[d] 11.6% of the total skin surface (USEPA, 2011).
[e] 11.2% of the total skin surface of a 2-year old (USEPA, 2011).

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, 2010). In the guideline scenario exposure assessment, it is assumed that WHO recommendations and product label instructions are followed. WHO recommends that operators wear an overall for indoor residual spraying.

In the lax standard scenario, 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.

The insecticide 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 suspensions) 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). The 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 total exposure time is 4 h: 160 minutes actual spray operation (120 L/day divided by 0.75 L/min) + 80 minutes other in-dwelling activity, totalling 240 minutes exposed to spray. 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 (L) and the wall surface is treated with 40 mL of spray solution to 1 m^2 (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 m^2 and 200 m^2; the default room size used in the calculations is 4 m × 4 m × 2.5 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, 2007, 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) is 0.07 mg a.i./kg a.i and that for insecticide packaged in water soluble bags is 0.04 mg a.i./kg a.i (USEPA, 2012).

The concentration of the spray liquid is to be checked from the 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, 2018; USEPA, 2012; HEEG, 2013b). 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. hat, gloves and other protective clothing, for example, overalls 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 (hat, 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, providing 90% protection. In the lax standard scenario, it is assumed that no PPE 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, or at least covered with plastic sheets; and that food items are removed before applying the insecticide (WHO, 2007).

The exposure of residents will come from skin contact with sprayed surfaces, and from food which becomes contaminated by being placed on contaminated surfaces. It is assumed that adults and older children are exposed similarly. For toddlers, there is higher contact with the floor, and also hand to mouth activity to consider. For infants, breast milk is an additional potential source of exposure to some insecticides.

Use of empty product packages to store food items or drinking-water may lead to high exposures and even acute intoxications. The variability of such practices is large and the risks involved cannot be modelled meaningfully. Such misuses are not covered in this risk assessment.

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

Mixing and loading insecticide formulation

Operator exposure

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

Products may be solids or liquids. Default dermal exposure to liquid products during each mixing and loading session is given in Table 4.

For solid products, default dermal exposure values derived from USEPA standard operating procedures can be applied (USEPA, 2012).

Estimation of systemic dose from mixing and loading for solid and liquid formulations is presented in Boxes 1 and 2.

Solid formulations

Box 1. Mixing and loading, dermal exposure; solid formulations	
$SysD_{TWA}$ =	$UE_{SOL} \times PPE \times ML \times Abs_D \times EF / (BW \times AT)$
$SysD_{MAX}$ =	$UE_{SOL} \times PPE \times ML \times Abs_D / BW$, *where*
$SysD_{TWA}$ =	TWA systemic dose (mg kg_{bw}^{-1})
$SysD_{MAX}$ =	Maximal daily systemic dose (mg kg_{bw}^{-1})
UE_{SOL} =	Unit exposure for a solid formulation, mg/kg a.i. handled (9.7 for wettable powders, 0.07 for water-dispersible granules, 0.04 for insecticide in water-soluble bags
PPE =	PPE efficacy 0.1 (90% protection) in guideline scenario, 1 (no protection) in lax standard scenario
ML =	amount of insecticide (a.i.) handled per day; default 12 loads per day, 10 L tank, concentration of the a.i. in the spray from the product label and dilution for spraying
Abs_D =	Dermal absorption for concentrated product (see section 4.1.3)
EF =	Exposure frequency (6 day/week, 6 weeks per treatment round, 2 rounds/yr = 72 d/yr)
BW =	Body weight (60 kg; Table 3)
AT =	Averaging time (365 d)

Liquid formulations

Box 2. Mixing and loading, dermal exposure; liquid formulations	
$SysD_{TWA}$ =	$UE_{LIQ} \times PPE \times CF \times NOD \times Abs_D \times EF / (BW \times AT)$
$SysD_{MAX}$ =	$UE_{LIQ} \times PPE \times CF \times NOD \times Abs_D / BW$, *where*
$SysD_{TWA}$ =	TWA systemic dose (mg kg_{bw}^{-1})
$SysD_{MAX}$ =	Maximal daily systemic dose (mg kg_{bw}^{-1})
UE_{LIQ} =	Unit exposure for a liquid formulation mL/operation (Table 4)
PPE =	PPE efficacy 0.1 (90% protection) in guideline scenario, 1 (no protection) in lax standard scenario
CF =	Concentration of formulation mg/mL (product label)
NOD =	Number of operations per day (default, 12)
Abs_D =	Dermal absorption for concentrated product (see section 4.1.3)
EF =	Exposure frequency (6d/week, 6 weeks per treatment round, 2 rounds/yr = 72 d/yr)
BW =	Body weight (60 kg; Table 3)
AT =	Averaging time (365 d)

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

Inhalation exposure

Inhalation exposure is dominated by exposure to the spray; exposure through volatilized, gaseous insecticide is not considered significant. The estimation is based on a target concentration (from the package label) sprayed/m^2 in a 4 m × 4 m × 2.5 m dwelling. Thus a total amount sprayed is 4 m × 4 m x 2.5 m = 40 m^2 × the target concentration in mg a.i./m^2. Of the sprayed active ingredient, 0.1% is assumed to be evenly distributed in the room, i.e. in a volume of 40 m^3.The concentration of the a.i.(mg/m^3) thus will be 0.001 × the target concentration (mg/m^2) on the wall.

In the guideline scenario, respiratory protection equipment (face mask) is assumed to give 90% protection.

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

The inhalation exposure during application may be calculated as shown in Box 3.

Box 3. Application, inhalation exposure

$SysD_{TWA}$ = $10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs_P \times EF / (BW \times AT)$
$SysD_{MAX}$ = $10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs_P / BW$, where

$SysD_{TWA}$ = TWA systemic dose (mg kg_{bw}^{-1})
$SysD_{MAX}$ = Maximal daily systemic dose (mg kg_{bw}^{-1})

TC_{WALL} = target amount of the a.i. on the wall, mg/m^2
RPE = protection provided by the respiratory protective equipment, 0.1 for the guideline scenario, 1.0 for the lax standard scenario
BV = breathing volume (moderate activity; default 1.25 m^3/h (Table 3))
ED = Exposure duration, 4 hours of spraying during the 8-h working day
Abs_P = Absorption from the respiratory tract. The default value is 100%
EF = Exposure frequency (6d/week, 6 weeks per treatment round, 2 rounds/yr = 72 d/yr)
BW = body weight (60 kg)
AT = averaging time, 1 year (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.

The dermal exposure during application, washing and maintenance may be calculated as shown in Box 4.

Box 4. Application, washing and maintenance. Dermal exposure

$SysD_{TWA}$ = $VS_{dermal} \times C_{spray} \times PPE \times EF \times Abs_D / (BW \times AT)$
$SysD_{MAX}$ = $VS_{dermal} \times C_{spray} \times PPE \times Abs_D / BW$

$SysD_{TWA}$ = TWA systemic dose (mg kg_{bw}^{-1})
$SysD_{MAX}$ = Maximal daily systemic dose (mg kg_{bw}^{-1})
VS_{dermal} = volume of spray on hands = 8.2 mL (see section 4.2.1)
C_{spray} = concentration of the active ingredient in the spray in mg/mL, derived from the concentration of the active ingredient in the formulation and its dilution for spraying
PPE = protection provided by the protective equipment, 0.1 for the guideline scenario, 1.0 for the lax standard scenario
EF = Exposure frequency (6 d/week, 6 weeks per treatment round, 2 rounds/yr = 72 d/yr)
Abs_D = dermal absorption of the spray (see section 4.1.3)
BW = body weight (60 kg)
AT = averaging time, 1 year (365 days)

Residential exposure

Post-application inhalation exposure is considered negligible owing to rapid loss of airborne aerosol and low volatility. For highly volatile active and toxic ingredients such as organophosphates of high toxicity (which are not recommended for use in residual treatments), it may be relevant to estimate inhalation exposure. In order to estimate the need to evaluate this exposure, the worst-case of exposure (a toddler staying 24 hours/day at a saturated vapour pressure concentration) of the pesticide can be estimated (HEEG, 2013b) as:

systemic dose = 0.328 × MM × VP, where

MM = molecular mass of the pesticide, and
VP, its vapour pressure at 25 °C (Pa).

In cases in which the estimated maximal exposure is significant, i.e. > 10% of the TSD, there is a need to perform a detailed assessment of the inhalation exposure to volatilized a.i.[1] This approach is only valid if aerosols are rapidly lost from the air.

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 (via contact with contaminated shelves), and also loosen from walls and generate house dust leading to ingestion by toddlers. For products that are toxic and are extensively excreted in mother's milk, 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 m^2 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

[1] In a limited study cyfluthrin concentrations were measured in the air in a non-ventilated room (36.7 m^3), where a 9.5 m^2 net impregnated with 50 mg/m^2 cyfluthrin (vapour pressure 2.1 µPa) was hanged for several days; there was no air exchange. The highest observed concentration was 0.055 µg/m^3. The evaporation area of the net (two-sided) was = 19 m^2. The WHO RA standard room of is 10 x 10 x 2 m = wall surface 80m^2 and volume 200 m^3. Assuming that the room temperature is approx.. 25°, that the air-borne concentration of an insecticide is directly proportional to the vapour pressure, and evaporation surface area and surface concentration, and inversely proportional to the volume of the evaporation space, the predicted concentration (µg/m^3) in of an insecticide will be

0.055 x 36.7 x VP µPa x TC mg/m^2 x EvapArea m^2/ (2.1 x 50 x 19 x Room volume m^3)

In the model standard room, (4 x 4 x 2.5 m), the volume is 40 m^3, and the wall surface is 40 m^2, and thus the predicted a.i. concentration µg/m^3 is 1.01 x 10-3 x VP x TC
(TC = target concentration on the walls)

contact is 15% of the wall target concentration (10% of the contact with the walls, 90% with the floors and furniture).[1]

The body part surface areas are given in Table 3. For adults and children it is assumed that the hands, forearms and feet are exposed; the area exposed is thus 0.308 m^2 for adults and 0.153 m^2 for children. For toddlers (aged 1–2 years), the hands, forearms, lower legs and feet (0.133 m^2) are assumed to be exposed. Infant floor mobility increases from the age of 3–6 months (USEPA, 2012); the exposed skin area for infants aged 0–12 months is assumed to include the head, hands, arms, trunk, legs and feet, i.e. 0.394 m^2).

The dermal exposure from residents touching contaminated surfaces may be calculated as shown in Box 5.

Box 5. Residents; dermal exposure from touching contaminated surfaces

$SysD_{TWA}$ = $0.15 \times TC_{WALL} \times AV \times Transl \times ESA \times Abs_D / BW$

$SysD_{MAX}$ = $0.15 \times TC_{WALL} \times Transl \times ESA \times Abs_D / BW$, where

$SysD_{TWA}$ =	TWA systemic dose due to dermal exposure from indoor residual spraying, (mg kg_{bw}^{-1})
$SysD_{MAX}$ =	Maximal daily systemic dose due to dermal exposure after a spraying episode, (mg kg_{bw}^{-1})
TC_{WALL} =	target concentration on the wall
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)
$Transl$ =	fraction translodged onto skin; default 8% of the amount on the surface (USEPA, 2012; hard surfaces)
ESA =	Exposed skin areas are 0.308 m^2 for adults (hands, forearms and feet), 0.153 m^2 for 6–11-yr children (hands, forearms and feet), 0.133 m^2 for toddlers (hands, forearms, lower legs, feet) and 0.394 m^2 for infants (head, hands, arms, trunk, legs and feet) (Table 3)
Abs_D =	dermal absorption (see section 4.1.3)
BW =	body weight (adults 60 kg, older children 23.9 kg, toddlers 10 kg, infants 8 kg)

Ingestion exposure

Ingestion exposure is the result of consuming contaminated foodstuff. 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 8%; (USEPA, 2012); 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 T½ of 60 d, leading to an average concentration of 0.42 × the original concentration over the 6-month interval between sprayings. The surface area of food (daily intake) can be calculated from the daily volume of food eaten (2202, 1417, 1378 and 1074 g/day) for adults, children, toddlers and infants respectively (USEPA, 2011). The density of food is approximately 1 g/cm^3, assuming that "food" is a cube of which one surface, i.e. volume to the power ⅔, is in contact

[1] Floor concentration = 0.3 × TC × 0.5 m × 38 m/100 m^2 = 0.057 × T.
10% of the contact with the walls (concentration TC) and 90% with the floor (concentration 0.057 x TC)
Default concentration on surfaces = 0.15 x TC

with the shelf: the contaminated surface of food is 0.0169 m^2 for adults, 0.0126 m^2 for children, 0.0124 m^2 for toddlers and 0.0105 m^2 for infants. Half of the food is in contact with the shelf (the rest is assumed to be either in bags or other wrappings, or peeled before use). Exposure is continuous.

The exposure from ingestion of contaminated food may be calculated as shown in Box 6.

Box 6. Residents; ingestion exposure from contaminated food

$SysD_{TWA}$ = $0.30 \times 0.5 \times AV \times TC_{WALL} \times Transl \times SAF \times Abs_O / (BW)$

$SysD_{MAX}$ = $0.30 \times 0.5 \times TC_{WALL} \times Transl \times SAF \times Abs_O / BW$, where

$SysD_{TWA}$	=	TWA systemic dose due to oral exposure from eating contaminated food, (mg kg_{bw}^{-1})
$SysD_{MAX}$	=	Maximal daily systemic dose due to oral exposure from eating contaminated food, (mg kg_{bw}^{-1})
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_{WALL}	=	target concentration on the wall surface mg/m^2
Transl	=	fraction translodged onto food. Default = 8% of the amount present on the surfaces (USEPA, 2012)
SAF	=	surface area of food in contact with the shelf, m^2 (0.0169, 0.0126, 0.0124 and 0.0105 m^2 for adults, children, toddlers and infants, respectively). Half of food items are in contact with contaminated surfaces
Abs_O	=	gastrointestinal absorption (default 100%)
BW	=	body weight (adults 60 kg, older children 23.9 kg, toddlers 10 kg, infants 8 kg)

Hand-to-mouth activity of the toddler

Box 7. Resident toddler; hand-to-mouth activity

$SysD_{TWA}$ = $0.15 \times AV \times TC_{WALL} \times Transl \times ESA \times F_{HM} \times F_{EXS} \times Abs_O / BW$

$SysD_{MAX}$ = $0.15 \times TC_{WALL} \times Transl \times ESA \times F_{HM} \times F_{EXS} \times Abs_O / BW$, where

$SysD_{TWA}$	=	TWA systemic dose due to oral exposure from hand-to-mouth activity, (mg kg_{bw}^{-1})
$SysD_{MAX}$	=	Maximal daily systemic dose due to oral exposure from hand-to-mouth activity, (mg kg_{bw}^{-1})
AV	=	average proportion of spray residue on the wall during 6 months of first-order kinetics' decay with a half-time of 60 days (0.42)
TC_{WALL}	=	target concentration on the wall surface mg/m^2
Transl	=	fraction translodged onto hands. Default = 8% of the amount present on the surfaces (USEPA, 2012)
ESA	=	exposed skin area (0.023 m^2; Table 3)
F_{HM}		F_{HM} = fraction of hand area mouthed; default 0.164 (USEPA, 2012; 75th percentile)
F_{EXS}		Fraction extracted in saliva; default 0.57 (USEPA, 2012; 75th percentile)
Abs_O	=	gastrointestinal absorption (default 100%)
BW	=	body weight (toddlers 10 kg)

Toddlers frequently put different objects in their mouths and ingest soil or dust from contaminated hands. It is estimated that 8% of the insecticide on contact surfaces is transferred onto hands and that 16.4% of the hand surface is mouthed (USEPA, 2012). The hand area of a child aged 1–2 years is 0.023 m^2 (USEPA, 2011). Saliva

is assumed to extract 57% of the chemical on mouthed hand surface (75th percentile; USEPA, 2012).

The ingestion exposure of toddlers from hand-to-mouth activity may be calculated as shown in Box 7. Hand-to-mouth behaviour and other activities carried out by toddlers may also cause ingestion of house dust. After indoor residual spraying, 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/m^2. The "upper percentile" (for 3–6 year olds) of dust eaten is 100 mg/day (USEPA, 2011); thus the daily dose of a 10 kg toddler would be 1 mg/kg × 100 mg/day / 10 kg bw = 0.01 µg/kg bw/day. 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.

Exposure via breast milk

Exposure via breast milk is estimated for a newborn, representing a worst-case scenario. If the estimated dose for the newborn is significant, exposure is estimated also for an infant.

When information is available on the fraction of the mother's dose excreted in her milk, this can be used to estimate the dose of the breast-fed infant. When extrapolating from animal data, the IPCS default variability factor for kinetics, $10^{0.6}$ = 3.98, is applied (WHO, 1999a) (Box 8).

Box 8. Exposure via breast milk estimated from fraction of dose excreted in milk

$SysD_{TWA} = 3.98 \times Fr_{milk} \times Abs_O \times Dose_M / BW$

$SysD_{TWA}$	=	systemic dose of the breast-fed infant due to the excretion of the insecticide in mother's milk (mg kg_{bw}^{-1})
Fr_{milk}	=	Fraction of the dose excreted in milk in an experimental animal
Abs_O	=	Oral absorption rate (default, 100%)
$Dose_M$	=	Dose the mother has received mg [estimated dose mg/kg bw x body weight of the mother kg]
BW	=	Body weight (newborn, 4.2 kg; infant, 8 kg) (Table 3)

When data on actual excretion in milk are not available, an upper bound of the exposure from mother's milk can be roughly estimated from the physicochemical characteristics, and kinetics of the insecticide as follows (Box 9).

Concentration of the insecticide in breast milk is estimated from the exposure of the mother at steady state. Body burden = daily dose mg/kg bw × T½ (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 × T½ (days)/ln(2) (SolC = 2.02 in Box 9). For lipid-soluble compounds (pKow ≥ 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. Thus the concentration in mother's milk for a fat-soluble chemical is 5 × mother's daily dose × 0.05 / ln (2) = 0.361 × dose of the mother (SolC in Box 9).

Box 9. Exposure via breast milk estimated from kinetic properties

$SysD_{TWA}$ = $SolC \times Dose_{Mbw} \times T½ \times IR \times Abs_O / BW$, *where*

$SysD_{TWA}$	=	TWA systemic daily dose (mg kg_{bw}^{-1})
SolC	=	Solubility constant; 2.02 for water-soluble and 0.361 for lipid-soluble insecticides
$Dose_{Mbw}$	=	daily dose to the mother (mg kg_{bw}^{-1})
T½	=	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
IR	=	ingestion rate of milk, kg/day, is 660 mL/day (average of mean values for the first 12 months; 510 mL for the first month (USEPA, 2011)
Abs_O	=	fraction absorbed (default is 100%)
BW	=	body weight (infant, 8 kg; newborn 4.2 kg; USEPA 2011; HEEG 2013a)

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

The total systemic dose is calculated by summing the contributions via different routes.

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 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 time-weighted average (TWA) exposure with tolerable systemic doses (TSDs) defined in hazard assessment in all relevant exposure situations.

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

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

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

When these ratios are < 1, the health risk is considered to be acceptable. When either one is > 1, there are possible health risks, and the planned use in indoor residual spraying may be unacceptable. Application of chemical-specific data instead of model defaults may be sought to refine the risk assessment. In the case of operators 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.

Risk–benefit considerations

When aspects of a risk assessment of a particular insecticide are unfavourable, risk managers will want to consider risk–benefit aspects, such as the potential for toxicity compared with the potential benefits of preventing the vector-borne disease in question, alternative insecticides and other vector control options (see http://www.who.int/neglected_diseases/vector_ecology/en/ and http://www.who.int/malaria/areas/vector_control/en/).

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 a synthetic pyrethroid "X" is used as a model compound.

Generic risk assessment model	Worked example
1. Toxicity *Aim:* 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. 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: • dog oral 52-week study; • dog oral 13-week study; • rat oral 13-week study; and • rabbit dermal 3-week study.
1.8 Identify critical NOAEL(s) from pivotal	1.8 Critical NOAELs:

Generic risk assessment model	Worked example
studies for acute exposure and for longer-term (repeat-dose) exposure.	• dog oral 52-week study – NOAEL of 1.5 mg $kg_{bw}^{-1}d^{-1}$ and LOAEL of 3 mg $kg_{bw}^{-1}d^{-1}$, critical toxic effect being neurotoxicity; • rat oral 13-week study – NOAEL of 2.2 mg $kg_{bw}^{-1}d^{-1}$ with neurotoxicity at 6.7 mg $kg_{bw}^{-1}d^{-1}$ (LOAEL); • rabbit dermal 3-week study – NOAEL 20 mg $kg_{bw}^{-1}d^{-1}$ per day for systemic effects, skin irritation observed also at 2 and 20 mg $kg_{bw}^{-1}d^{-1}$.
1.9 Assess whether the database allows the setting of TSDs for short- and long-term exposure via oral, dermal and inhalational routes.	1.9 Database is adequate for the setting of TSDs for short- and long-term exposure. No data are available on inhalation exposure.
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 is recommended 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.	1.10 The ADI of 0–0.02 mg kg_{bw}^{-1} is set by WHO. This is based on the 52-week dog study showing a NOAEL of 1.5 mg $kg_{bw}^{-1}d^{-1}$ and applying a UF of 100. The oral absorption of X (Abs_{oral}) was 36%. Thus the TSD = 0.02 x 0.36 = 7.2 µg $kg_{bw}^{-1}d^{-1}$. WHO has set an ARfD of 0.04 mg $kg_{bw}^{-1}$for insecticide X. The TSD_{AC} thus is 0.04 x 0.36 = 14.4 µg kg_{bw}^{-1}.
1.11 Conclusion on final TSD(s)	1.11 TSD used in risk characterization: • 7.2 µg $kg_{bw}^{-1}d^{-1}$ for total systemic exposure; • TSD_{AC} = 14.4 µg kg_{bw}^{-1}.
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. The target concentration of the a.i. on the wall is 32 mg/m^2, the application rate is 40 mL/m^2 and the spray is diluted to a concentration of 32/40 = 0.8 mg/mL or 8 g/10 L. Eight grams of X is diluted into a 10-L volume in a spray tank and the amount of X thus handled per day (12 tank loads) will be 96 g or 0.096 kg. The molecular mass of X is 416.3 and vapour pressure is 0.34 x 10^{-6} Pa. Thus the worst case systemic dose of a toddler (24 h/d in saturated X vapour) would be < 1% of the TSD and exposure to volatilized X need not be considered (see section 4.2.2). The oral absorption of X in humans has been reported to be 36%, and the dermal absorption of a diluted solution of X, 1.2%. No data were available on the dermal absorption of concentrated X (thus the figure for diluted X was used throughout) or excretion of X in milk; the half-time of X in humans was approximately 24 h.	
2.1 Operator exposure	
a) *Mixing and loading, inhalation exposure*	In mixing and loading, inhalation exposure is negligible.
b) *Mixing and loading, dermal exposure* *Predicted TWA systemic dose* $SysD_{TWA} = UE_{SOL} \times PPE \times ML \times Abs_D \times EF / (BW \times AT)$ *Predicted maximal daily systemic dose* $SysD_{MAX} = UE_{SOL} \times PPE \times ML \times Abs_D / BW$ UE_{SOL} = unit exposure for WP = 9.7 mg a.i. /kg	<u>Guideline scenario</u> Predicted TWA systemic dose $SysD_{TWA}$ = 9.7 x 0.1 x 0.096 x 0.012 x 72 / (60 x 365) **= 0.004 µg $kg_{bw}^{-1}d^{-1}$** Predicted maximal daily systemic dose $SysD_{MAX}$ = 9.7 x 0.1 x 0.096 x 0.012 / 60 **= 0.019 µg kg_{bw}^{-1}** <u>Lax standard scenario</u> Predicted TWA systemic dose $SysD_{TWA}$

Generic risk assessment model	Worked example
handled *PPE* = 0.1 for guideline scenario, 1.0 for lax standard scenario *ML* = Amount of a.i. handled per day = 0.096 kg Abs_D = Dermal absorption = 1.2% *EF* = 72 d/yr *BW* = *60* kg *AT* = 365 d/yr	= 9.7 x 1 x 0.096 x 0.012 x 72 / (60 x 365) **= 0.037 µg $kg_{bw}^{-1}d^{-1}$** Predicted maximal daily systemic dose $SysD_{MAX}$ = 9.7 x 1 x 0.096 x 0.012 / 60 **= 0.186 µg kg_{bw}^{-1}**
c) Application, inhalation exposure *Predicted TWA systemic dose* $SysD_{TWA}$ = $10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs_P \times EF / (BW \times AT)$ *Predicted maximal daily systemic dose* $SysD_{MAX}$ = $10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs_P / BW$ TC_{WALL} = 32 mg/m^2 *RPE = 0.1 for guideline scenario; 1 for lax standard scenario* *BV* = 1.56 m^3/h *ED* = 4 h Abs_P = 100% *EF* = 72 d/yr *BW* = 60 kg *AT* = 365 d/yr	<u>Guideline scenario</u> Predicted TWA systemic dose $SysD_{TWA}$ = 10^{-3} x 32 x 0.1 x 1.56 x 4 x 1 x 72 / (60 x 365) **= 0.066 µg $kg_{bw}^{-1}d^{-1}$** Predicted maximal daily systemic dose $SysD_{MAX}$ = 10^{-3} x 32 x 0.1 x 1.56 x 4 x 1 / 60 **= 0.333 µg kg_{bw}^{-1}** <u>Lax standard scenario</u> Predicted TWA systemic dose $SysD_{TWA}$ = 10^{-3} x 32 x 1 x 1.56 x 4 x 1 x 72 / (60 x 365) **= 0.656 µg $kg_{bw}^{-1}d^{-1}$** Predicted maximal daily systemic dose $SysD_{MAX}$ = 10^{-3} x 32 x 1 x 1.56 x 4 x 1 / 60 **= 3.33 µg kg_{bw}^{-1}**
d) Dermal exposure during application and washing and maintenance of the equipment $SysD_{TWA}$ = $VS_{dermal} \times C_{spray} \times PPE \times EF \times Abs_D /(BW \times AT)$ $SysD_{MAX}$ = $VS_{dermal} \times C_{spray} \times PPE \times Abs_D /BW$ VS_{dermal} = 8.2 mL C_{spray} = 0.8 mg/mL *PPE = 0.1 for guideline scenario, 1 for lax standard scenario* *EF* = 72 Abs_D = 1.2% *BW* = 60 kg *AT* = 365	<u>Guideline scenario</u> Predicted TWA systemic dose $SysD_{TWA}$ = 8.2 x 0.8 x 0.1 x 72 x 0.012 / (60 x 365) **= 0.026 µg $kg_{bw}^{-1}d^{-1}$** Predicted maximal daily systemic dose $SysD_{MAX}$ = 8.2 x 0.8 x 0.1 x 0.012 / 60 **= 0.131 µg kg_{bw}^{-1}** <u>Lax standard scenario</u> Predicted TWA systemic dose $SysD_{TWA}$ = 8.2 x 0.8 x 1 x 72 x 0.012 / (60 x 365) **= 0.259 µg $kg_{bw}^{-1}d^{-1}$** Predicted maximal daily systemic dose $SysD_{MAX}$ = 8.2 x 0.8 x 1 x 0.012 / 60 **= 1.312 µg kg_{bw}^{-1}**
e) Total operator predicted dose Dermal and inhalation exposure from mixing, loading, spraying, and washing and maintenance of the equipment added together.	<u>TWA systemic dose</u> Guideline scenario: 0 + 0.004 + 0.066 + 0.026 **= 0.096 µg $kg_{bw}^{-1}d^{-1}$** Lax standard scenario: 0 + 0.037 + 0.656 + 0.259 **= 0.952 µg $kg_{bw}^{-1}d^{-1}$** <u>Total predicted maximal daily dose</u> Guideline scenario: 0 + 0.019 + 0.333 + 0.131 **= 0.483 µg kg_{bw}^{-1}**

Generic risk assessment model	Worked example
	Lax standard scenario: 0+0.186+3.33+1.312 **= 4.828 µg kg_{bw}^{-1}**
2.2 Residential exposure	
a) Dermal exposure due to touching contaminated surfaces *SysDTWA = 0.15× TCWALL × AV × Transl × ESA × AbsD / BW* *SysDMAX = 0.15 × TCWALL × Transl × ESA × AbsD / BW* *TCWALL = target concentration on the wall; 32 mg/m2* *AV* = Average concentration over a 6-month period; 0.42 *Transl* = transfer from contaminated surface onto skin; 0.08 *ESA* = exposed skin area; 0.308 m^2 for adults; 0.153m^2 for children; 0.133 m^2 for toddlers Abs_D = dermal absorption, 0.012 *BW* = body weight 60 kg for an adult, 23.9 kg for a child and 10 kg for a toddler	Predicted TWA systemic dose $SysD_{TWA}$ Adults = 0.15 x 32 x 0.42 x 0.08 x 0.308 x 0.012 / 60 **= 0.010 µg $kg_{bw}^{-1}d^{-1}$** Children = 0.15 x 32 x 0.42 x 0.08 x 0.153 x 0.012 / 23.9 **= 0.012 µg $kg_{bw}^{-1}d^{-1}$** Toddlers = 0.15 x 32 x 0.42 x 0.08 x 0.133 x 0.012 / 10 **= 0.026 µg $kg_{bw}^{-1}d^{-1}$** Predicted maximal daily systemic dose $SysD_{MAX}$ Adults = 0.15 x 32 x 0.08 x 0.308 x 0.012 / 60 **= 0.024 µg kg_{bw}^{-1}** Children = 0.15 x 32 x 0.08 x 0.153 x 0.012 / 23.9 **0.029 µg kg_{bw}^{-1}** Toddlers: = 0.15 x 32 x 0.08 x 0.133 x 0.012 / 10 **= 0.061 µg kg_{bw}^{-1}**
b) Oral exposure contaminated foodstuffs *SysDTWA = 0.30 x 0.5 × AV × TCWALL × Transl × SAF × AbsO / BW* *SysDMAX = 0.30 x 0.5 × TCWALL × Transl × SAF × AbsO / BW* *AV* = average concentration over a 6-month period; 0.42 TC_{WALL} = target concentration on the wall; 32 mg/m^2 *Transl* = fraction transloged onto food; 0.08 *SAF* = surface area of food, 0.0169 for adults, 0.0126 for children; 0.0124 for toddlers and 0.0105 m^2 for infants Abs_O = oral absorption, 0.36 *BW* = body weight, adults 60 kg, children 23.9 kg, toddlers 10 kg, infants 8 kg	Predicted TWA systemic dose exposure Adults $SysD_{TWA}$ = 0.30 x 0.5 x 0.42 x 32 x 0.08 x 0.0169 x 0.36 / 60 **= 0.0164 µg $kg_{bw}^{-1}d^{-1}$** Children = 0.30 x 0.5 x 0.42 x 32 x 0.08 x 0.0126 x 0.36 / 23.9 **= 0.0306 µg $kg_{bw}^{-1}d^{-1}$** Toddlers = 0.30 x 0.5 x 0.42 x 32 x 0.08 x 0.0124 x 0.36 / 10 **= 0.0720 µg $kg_{bw}^{-1}d^{-1}$** Infants = 0.30 x 0.5 x 0.42 x 32 x 0.08 x 0.0105 x 0.36 / 8 **= 0.0762 µg $kg_{bw}^{-1}d^{-1}$** Predicted maximal daily systemic dose *Adults* $SysD_{MAX}$ = 0.30 x 0.5 x 32 x 0.08 x 0.0169 x 0.36 / 60 **= 0.0389 kg_{bw}^{-1}** Children = 0.30 x 0.5 x 32 x 0.08 x 0.0126 x 0.36 / 23.9 **= 0.0729 µg kg_{bw}^{-1}** Toddlers: = 0.30 x 0.5 x 32 x 0.08 x 0.0124 x 0.36 / 10 **= 0.171 µg kg_{bw}^{-1}**

Generic risk assessment model	Worked example
	Infants: = 0.30 x 0.5 x 32 x 0.08 x 0.0105 x 0.36 / 8 **= 0.181 µg kg_{bw}^{-1}**
c) Ingestion exposure of toddlers via hand-to-mouth behaviour *SysDTWA = 0.15 × AV × TCWALL × Transl × ESA × FHM × FEXS × AbsO / BW* *SysDMAX = 0.15 × TCWALL × Transl × ESA × FHM × FEXS × AbsO / BW* *AV* = average concentration over a 6-month period; 0.42 TC_{WALL} = target concentration on the wall; 32 mg/m^2 *Transl* = transfer from contaminated surface onto skin; 0.08 *ESA* = exposed skin area; 0.023 m^2 F_{HM} = fraction of hand mouthed; 0.164 F_{EXS} = fraction extracted in saliva; 0.57 Abs_O = oral absorption; 0.36 *BW* = body weight; 10 kg	Predicted TWA systemic dose Toddlers = 0.15 x 0.42 x 32 x 0.08 x 0.023 x 0.164 x 0.57 x 0.36 / 10 **= 0.0125 µg $kg_{bw}^{-1}d^{-1}$** <u>Predicted maximal daily systemic dose</u> Toddlers: = 0.15 x 32 x 0.08 x 0.023 x 0.164 x 0.57 x 0.36 / 10 **= 0.0297 µg $kg_{bw}^{-1}d^{-1}$**
d) Ingestion exposure via breast milk, newborn $SysD_{TWA}$ = *SolC × $Dose_{Mbw}$ × T½ × IR × Abs_O / BW* $SysD_{TWA}$ = TWA systemic dose *SolC* = solubility constant; 0.361 *DoseM* = dose of the mother; **0.952 µg $kgbw^{-1}d^{-1}$** (operator; lax standard scenario) x 60 kg *T½* = half-time of X in the body; 1 day *IR* = *ingestion rate of mother's milk; 0.51 kg/day* Abs_O = oral absorption; 0.36 *BW* = body weight; 4.2 kg	Predicted TWA systemic dose exposure Newborn: = 0.361 x 0.952 x 60 x 0.51 x 0.36 / 4.2 **= 0.901 µg $kg_{bw}^{-1}d^{-1}$** These estimates of TWA exposure also represent maximal daily dose, as it is based on the steady- state body burden of the mother. The estimated systemic dose of the newborn (0–1 month) via breast milk is 13% of the TSD for a newborn of a mother doing indoor residual spraying in the lax standard scenario. The dose will be approximately 1% of the TSD in the guideline scenario. For comparison, doses for an infant (0–1 year) would be 0.7 % (guideline scenario) and 7% (lax standard scenario) of the TSD, indicating that the dose for newborns is the worst case.
e) Total predicted resident dose	d) Total TWA resident predicted dose Adult: 0.010 + 0.0164 **= 0.0264 µg $kg_{bw}^{-1}d^{-1}$** Child: 0.012 + 0.0306 **= 0.0426 µg $kg_{bw}^{-1}d^{-1}$** Toddler: 0.026 + 0.0720 + 0.0125 **= 0.111 µg $kg_{bw}^{-1}d^{-1}$** Infant: **= 0.0762 µg $kg_{bw}^{-1}d^{-1}$** Newborn: **= 0.901 µg $kg_{bw}^{-1}d^{-1}$** Total predicted maximal daily dose Adult: 0.024+0.0389 **= 0.0629 µg kg_{bw}^{-1}** Child: 0.029+0.0729 **= 0.102 µg kg_{bw}^{-1}** Toddler: 0.061+0.171+0.0297 **= 0.262 µg kg_{bw}^{-1}** Infant: **= 0.181 µg kg_{bw}^{-1}**
2.3 Residents participating in insecticide preparation and application Exposure of the residents who also apply the	The predicted TWA dose of resident operator: <u>Guideline scenario</u> 0.096 + 0.0264 **= 0.122 µg $kg_{bw}^{-1}d^{-1}$** <u>Lax standard scenario</u>

Generic risk assessment model	Worked example
insecticide is calculated by summing up the predicted doses for operators (mixing and loading plus application, washing and maintenance) and adult residents (eating contaminated foodstuff plus touching contaminated surfaces). It is assumed that only adults work as insecticide operators.	0.952 + 0.0264 **= 0.978 µg $kg_{bw}^{-1}d^{-1}$** The predicted maximal daily dose of resident operator: <u>Guideline scenario</u> 0.483 + 0.0629 **= 0.546 µg kg_{bw}^{-1}** <u>Lax standard scenario</u> 4.828+0.0629 **= 4.891 µg kg_{bw}^{-1}**
2.4 Reuse of contaminated pesticide product packages This represents a gross misuse, which definitely should be eliminated, and need only be taken into account in specific situations.	A solid formulation is used. Therefore, reusing the packages is not considered a relevant cause of exposure.
3. Risk characterization For products with appreciable acute toxicity or irritative properties, consideration should be given to acute reference doses. 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 that it does not cause unacceptable risk to human health. 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 must be implemented. In some cases the exposure is found unacceptable. Other methods of vector control should be considered.	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 mainly on comparison with the long-term toxicity and the long-term TSD. From 1.11 TSD used in subsequent risk characterization is: TSD = **7.2 µg $kg_{bw}^{-1}d^{-1}$**, and TSD_{AC} = **14.4 µg kg_{bw}^{-1}** <u>Operator exposure</u> Predicted doses to be used in subsequent risk characterization: Total TWA operator predicted doses: Guideline scenario: = 0.096 µg $kg_{bw}^{-1}d^{-1}$. Lax standard scenario: = 0.952 µg $kg_{bw}^{-1}d^{-1}$. In the guideline and lax standard scenarios, operator exposure is acceptable, **1.3%** and **13.2%** of the TSD. Total maximal operator systemic dose in the guideline scenario is 0.483 µg kg_{bw}^{-1} and in lax standard scenario is 4.828 µg kg_{bw}^{-1}. The maximal systemic dose of the operator is acceptable in the guideline scenario (**3.4%** of TSD_{AC}) and also in the lax standard scenario (**33.5%** of TSD_{AC}) <u>Resident exposure</u> Total resident predicted TWA systemic doses: Adults = 0.0264 µg $kg_{bw}^{-1}d^{-1}$ Adult resident exposure is considered acceptable. The predicted dose is **0.4%** of the TSD. Children = 0.0426 µg $kg_{bw}^{-1}d^{-1}$ Resident child exposure is considered

Generic risk assessment model	Worked example
	acceptable. The predicted dose is **0.6%** of the TSD. Toddlers = 0.111 µg $kg_{bw}^{-1}d^{-1}$
	Resident toddler exposure is considered acceptable. The predicted dose is **1.5%** of the TSD. Infants = 0.0762 µg $kg_{bw}^{-1}d^{-1}$ Resident infant exposure is considered acceptable. The predicted dose is **1.1%** of the TSD. Newborn babies – breast milk exposure. In the lax standard scenario, operator plus residential exposure, the predicted systemic exposure of the newborn = 0.901 µg $kg_{bw}^{-1}d^{-1}$ Exposure of newborn babies is considered acceptable. The predicted dose is **13%** of the TSD. The maximal daily dose of residents is acceptable, **0.4, 0.7, 1.8, and 1.3%** of the TSD_{AC} for adults, children, toddlers, and infants, respectively. <u>Residents who also work as spray operators</u> Predicted TWA dose in guideline scenario = 0.122 µg $kg_{bw}^{-1}d^{-1}$ Predicted TWA dose in lax standard scenario = 0.978 µg $kg_{bw}^{-1}d^{-1}$ Exposure of residents working as spray operators in the guideline and lax standard scenarios is considered acceptable. The predicted exposure is **1.7%** and **6.8%** of the TSD, respectively. Predicted maximal daily dose in guideline scenario = 0.546 µg kg_{bw}^{-1} Predicted dose in lax standard scenario = 4.891 µg kg_{bw}^{-1} Exposure of residents working as spray operators in the guideline and lax standard scenarios is considered acceptable. The predicted exposure is **4%** and **34%** of the TSD, respectively.

7. References

Bhat VS et al (2017). Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; Increasing utility and facilitating regulatory acceptance. Crit Rev Toxicol. 47(9):729–49.

Dorne JLCM and Renwick AG (2005). The refinement of uncertainty/safety factors in risk assessment by the incorporation of data on toxicokinetic variability in humans. Toxicol Sc. 86(1):20–26.

Dourson ML, Knauf LA, Swartout JC (1992). On reference dose (RfD) and its underlying toxicity data base. Toxicol Ind Health. 8(3):171–89.

EFSA (2011). EFSA Panel on Plant Protection Products and their Residues (PPR); EFSA Scientific Opinion on the science behind the revision of the guidance document on dermal absorption. EFSA Journal. 9(7):2294 (http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2294/epdf, accessed 28 February 2018).

EFSA (2012). Guidance on dermal absorption. Scientific Opinion. EFSA Panel on plant protection products and their residues (PPR). Parma, Italy: EFSA Journal. 10(4):2665 (http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2665/epdf, accessed 28 February 2018).

EFSA (2014). Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal. 12(10):3874 (http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3874/pdf, accessed 28 February 2018).

EU (2006). Draft guidance for the setting and application of acceptable operator exposure levels (AOELs) (http://ec.europa.eu/food/plant/docs/pesticides_ppp_app-proc_guide_tox_accpt-exp-levs-2006.pdf).

EUROPOEM (2003). The development, maintenance and dissemination of a European Predictive Operator Exposure Model (EUROPOEM) database. A EUROPOEM II Database and Harmonised Model, FAIR3-CT96-1406. Carshalton, England: TNO-BIBRA International.

FAO/WHO (2014). The International Code of Conduct on Pesticide Management. Rome: Food and Agriculture Organization of the United Nations and Geneva: World Health Organization (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/CODE_2014Sep_ENG.pdf, accessed 28 February 2018).

HEEG (2013a). Default human factor values for use in exposure assessments for biocidal products. HEEG Opinion [endorsed at TM II 2013]. Brussels: European Commission Joint Research Centre, Institute for Health and Consumer Protection, Chemical assessment and testing (https://echa.europa.eu/documents/10162/19680902/heeg_opinion_17_default_human_factor_values_en.pdf, accessed 28 February 2018).

HEEG (2013b). Assessment of inhalation exposure of volatilised biocide active substances. HEEG Opinion 13 [endorsed at TM IV 2011 and amended after TM III 2013 to take into account changed default human factor values]. Brussels: European Commission Joint Research Centre, Institute for Health and Consumer Protection, Chemical assessment and testing (https://echa.europa.eu/documents/10162/19680902/heeg_opinion_13_volatilised_inhalation_exposure_en.pdf, accessed 28 February 2018).

Herrman JL, Younes M (1999). Background to the ADI/TDI/PTWI. Regul Toxicol Pharmacol. 30:S109–13. doi:10.1006/rtph.1999.1335.

JECFA (2002). Safety evaluation of certain food additives and contaminants / prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva: World Health Organization [WHO Food Additives Series, No. 48] (http://www.inchem.org/documents/jecfa/jecmono/v48je20.htm, accessed 28 February 2018).

JMPM (2008). 2nd FAO/WHO Joint Meeting on Pesticide Management and 4th Session of the FAO Panel of Experts on Pesticide Management, Geneva, 6–8 October 2008. Rome: Food and Agriculture Organization of the United Nations and Geneva: World Health Organization (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/Report.pdf, accessed 28 February 2018).

JMPR (1982). Bendiocarb. PESTICIDE RESIDUES IN FOOD – 1982. Sponsored jointly by FAO and WHO (http://www.inchem.org/documents/jmpr/jmpmono/v82pr05.htm, accessed 28 February 2018).

JMPR (1984). Bendiocarb. PESTICIDE RESIDUES IN FOOD – 1984. Sponsored jointly by FAO and WHO (http://www.inchem.org/documents/jmpr/jmpmono/v84pr45.htm, accessed 28 February 2018).

JMPR (1998a). Report of the Joint Meeting of the FAO Panel of Experts on Pesticide residues and the Environment and the WHO Core Assessment Group, Rome 21–30 September 1998. Geneva: World Health Organization (www.who.int/pcs/jmpr/jmpr.htm): Section 2.14, Interpretation of cholinesterase inhibition:17–19.

JMPR (1998b). Report of the Joint Meeting of the FAO Panel of Experts on pesticide residues and the environment and the WHO Core Assessment Group, Rome 21–30 September 1998. Geneva: World Health Organization (available at www.who.int/pcs/jmpr/jmpr.htm): Section 2.13, Procedures for estimating an acute reference dose:14–17.

JMPR (1999). Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group, Rome, 20–29 September 1999 (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/REPORT1999.pdf, accessed 28 February 2018).

JMPR (2008). Safety factors for acute C_{max}-dependent effects: specific considerations with respect to carbamates such as carbofuran. In: Pesticide residues in food – 2008. Joint FAO/WHO meeting on pesticide residues. Evaluations 2008 Part II Toxicological: 7–10 (http://whqlibdoc.who.int/publications/2010/9789241665247_eng.pdf, accessed 28 February 2018).

JMPR (2012). Inventory of evaluations performed by the Joint Meeting on Pesticide Residues (JMPR) (http://apps.who.int/pesticide-residues-jmpr-database, accessed 28 February 2018).

Meek ME et al (2011). Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regul Toxicol Pharmacol. 60:S1–14.

Nordic Council of Ministers (2007). Probabilistic exposure assessment methods in chemical safety assessments (REACH). Copenhagen: Nordic Council of Ministers (TemaNord 2007:563; http://norden.diva-portal.org/smash/get/diva2:702703/FULLTEXT01.pdf, accessed 28 February 2018).

OECD (2011). Guidelines for the testing of chemicals (and subsequent revisions). Paris: Organisation for Economic Cooperation and Development (http://www.oecd-

ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals_chem_guide_pkg-en;jsessionid=j73j4wz0ptk0.delta, accessed 28 February 2018).

PSD (2007). UK Predictive Operator Exposure Model (POEM): a user's guide. York (UK): Pesticides Safety Directorate (available at: http://www.pesticides.gov.uk/approvals.asp?id=2427, accessed 28 February 2018).

SCHER (2011). Toxicity and assessment of chemical mixtures. Scientific Committee on Health and Environmental Risks (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Scientific Committee on Consumer Safety (SCCS). Brussels: European Commission Directorate-General for Health & Consumers (http://ec.europa.eu /health/scientific_committees/environmental_risks/docs/scher_o_155.pdf, accessed 28 February 2018).

Solecki R, Davies L, Dellarco V, Dewhurst I, Raaij Mv, Tritscher A (2005). Guidance on setting of acute reference dose (ARfD) for pesticides. Food Chem Toxicol. 43:1569–93. doi:10.1016/j.fct.2005.04.005.

UN (2015). Globally harmonized system of classification and labelling of chemicals (GHS), 6th revised edition. New York (NY): United Nations (http://www.unece.org/fileadmin/ DAM/trans/danger/publi/ghs/ghs_rev06/English/ST-SG-AC10-30-Rev6e.pdf, accessed 28 February 2018).

USEPA (2010). Final test guidelines for pesticides and toxic substances. Washington (DC): United States Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention (https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/final-test-guidelines-pesticides-and-toxic, accessed 28 February 2018).

USEPA (2011). Exposure factors handbook 2011 edition (final report). Washington (DC): United States Environmental Protection Agency, Office of Research and Development C (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252, accessed 28 February 2018).

USEPA (2012). Standard operating procedures for residential pesticide exposure assessment. Washington (DC): United States Environmental Protection Agency, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedure-residential-exposure, accessed 28 February 2018)

Vermeire T et al. (1999). Assessment factors for human health risk assessment: a discussion paper. Crit Rev Toxicol. 29(5):439–90. doi:10.1080/10408449991349249.

WHO (1994). Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. Geneva: World Health Organization (Environmental Health Criteria 170; http://www.inchem.org/documents/ehc/ehc/ehc170.htm, accessed 28 February 2018).

WHO (1999). Principles for the assessment of risks to human health from exposure to chemicals. Geneva: World Health Organization (Environmental Health Criteria 210; http://www.inchem.org/documents/ehc/ehc/ehc210.htm, accessed 28 February 2018).

WHO (2005a). Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration-response assessment. Geneva, World Health Organization (Harmonization Project Document No. 2; available at:http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf, accessed 28 February 2018).

WHO (2005b). Principles of characterizing and applying human exposure models. Geneva: World Health Organization (Harmonization Project Document No. 3; http://apps.who.int/iris/bitstream/10665/43370/1/9241563117_eng.pdf, accessed 28 February 2018).

WHO (2007). Manual for indoor residual spraying: application of residual sprays for vector control, 3rd edition. Geneva: World Health Organization (http://apps.who.int/iris/bitstream/10665/69664/1/WHO_CDS_NTD_WHOPES_GCDPP_2007.3_eng.pdf, accessed 28 February 2018).

WHO (2008). Part 1: Guidance document on characterizing and communicating uncertainty in exposure assessment. Geneva: World Health Organization (Harmonization Project Document No. 6; http://www.who.int/ipcs/methods/harmonization/areas/uncertainty%20.pdf, accessed 28 February 2018).

WHO (2009a). Principles for modelling dose–response for the risk assessment of chemicals. Geneva: World Health Organization (Environmental Health Criteria 239; http://whqlibdoc.who.int/publications/2009/9789241572392_eng.pdf, accessed 28 February 2018).

WHO (2009b). Principles and methods for the risk assessment of chemicals in food. Geneva: World Health Organization (Environmental Health Criteria 240 (http://www.who.int/foodsafety/publications/chemical-food/en/, accessed 28 February 2018).

WHO (2010). Equipment for vector control: specification guidelines, revised edition. Geneva: World Health Organization (http://whqlibdoc.who.int/publications/2010/9789241500791_eng.pdf, accessed February 2018).

WHO (2018). A generic risk assessment model for insecticide-treated nets, 2nd edition. Geneva: World Health Organization (http://apps.who.int/iris/bitstream/10665/260305/1/9789241513586-eng.pdf, accessed 28 February 2018).

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