World Health Organization

2nd EDITION

GENERIC RISK ASSESSMENT MODEL FOR INSECTICIDE-TREATED NETS

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Based on experience accumulated and developments in net technology and exposure assessment methods, the document was revised by the WHO Secretariat and peer reviewed by its contact points in September 2016. Comments were received from the following: Tao Chuanjiang, Ministry of Agriculture, China; Jérémy De Saint-Jores, French agency for food, environmental and occupational health & safety (ANSES), France; Flore Cognat, European Chemical Industry Council (Cefic); Beyene Negatu Mormeta, Institute for Risk Assessment Sciences, University of Utrecht, Netherlands; Naoko Nagasawa, Sumitomo Chemical Co. Ltd., Japan; Laurent Patty, Bayer CropScience, France; Patrick Rose, JSC International Limited, UK; Simon Scarrott, Health & Safety Executive, UK; Steve Smith, SC Johnson & Son, Inc., USA. The Secretariat then 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 WHO Secretariat that included Dr Richard Brown, WHO International Programme on Chemical Safety, and Dr Rajpal Yadav, Vector Ecology and Management, WHO Department of Control of Neglected Tropical Diseases. 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
BMD	benchmark dose
CIPAC	Collaborative International Pesticides Analytical Council
EU	European Union
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
ITN	insecticide-treated net – either conventionally treated and retreatable net or long-lasting net (LN)
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	tropical conditions are accommodated and no personal protection other than light clothing covering the trunk is assumed
LN	factory-treated long-lasting insecticidal net – not retreated by dipping
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation andDevelopment
OEL	occupational exposure limit
PSD	Pesticides Safety Directorate of the United Kingdom
RfD	reference dose
SOP	standard operating procedure
TSD	tolerable systemic dose
TSD_{AC}	tolerable systemic dose, acute exposure
TWA	time-weighted average
UF	uncertainty factor
USAID	United States Agency for International Development
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme

1. PURPOSE

Long-lasting insecticidal nets (LNs) constitute a core vector control intervention against malaria. A number of new LN products are under development and will require assessment of risks to humans. This document provides an updated generic model that can be used for the risk assessment of exposure to insecticides of individuals sleeping under LNs and during the washing of nets. In an Annex, exposures and health risks are described for the conventional treatment or retreatment of nets (ITNs) with an insecticide considering that such practices may still be used in evaluation of ITNs and their use. The generic model does not include the risks associated with the manufacturing of LNs in a factory environment.

2. BACKGROUND

2.1 Need for a generic risk assessment model

Pyrethroid insecticides have been extensively used for the treatment of nets to protect against malaria and other vector-borne diseases. The effectiveness of such nets in reducing morbidity and mortality from malaria is well documented (WHO, 2000; Lengeler, 2004). The WHO Global Malaria Programme has made LNs one of the two core interventions against malaria.

The WHO Pesticide Evaluation Scheme (WHOPES) has recommended certain insecticide formulations for the conventional treatment of nets, as shown on the WHOPES website (http://www.who.int/whopes/en/).

With the emergence and spread of pyrethroid resistance among insect vectors, new brands of LNs containing a mixture of a pyrethroid and a compound in an alternative insecticide class with a different mode of action have been evaluated and recommended by WHO. In future, LNs with new active ingredients may also be produced. A generic risk assessment model is therefore needed, that is applicable to mixture or combination LNs. The model should incorporate data on the use patterns and typical exposure scenarios associated with the use of LNs. At the same time, the conventionally treated nets (ITNs) may still be used and may become again more important in the future; the model encompasses the manual treatment of nets in an Annex. For treatment or retreatment of the nets, the model includes both the guideline scenario (in which the guidelines given are strictly followed) and a lax standard scenario (in which tropical conditions are accommodated and no personal protection other than light clothing covering the trunk of the impregnator is assumed).

2.2 Probabilistic vs. deterministic risk assessment models

Historically, exposure models have relied 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 risk assessment – of nets, 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). 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). A probabilistic risk assessment of five long-lasting pyrethroid-treated nets has been published (Peterson et al., 2011).

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).

2.3 Essential elements of a human health risk assessment model

Comprehensive presentations on the principles of risk assessment can be found elsewhere in the scientific literature (see, for example, WHO, 1999; 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, and other issues that are relevant in making operational decisions on the acceptability of a particular level of risk.

Risk assessments involve three steps:

1. *Hazard assessment*. Hazard assessment comprises hazard identification and hazard characterization, i.e. identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects occur, and the dose/exposure levels below which no adverse effects are observed.
2. *Exposure assessment*. Exposure assessment may concern 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 for all relevant exposure situations.

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

3. THE HEALTH RISK ASSESSMENT MODEL

3.1 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.

3.1.1 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 the insecticides, e.g. in the regulatory context of crop protection, 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 (https://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.

3.1.2 Types of health hazard data

Human data

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

- case reports of accidental and deliberate exposures and poisonings;
- epidemiological studies, including occupational studies on those manufacturing or using the 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 insecticide-treated net use and maintenance

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 - Environmental Health Criteria Monographs	http://www.who.int/ipcs/publications/cicad/en/ 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/index.php
United States Environmental Protection Agency (USEPA) – Pesticide evaluations	https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1
European Food Safety Authority (EFSA) – Pesticide Risk Assessments	http://www.efsa.europa.eu/en/pesticides/pesticidesscdocs.htm
European Chemicals Agency – Information on Chemicals search page	https://echa.europa.eu/information-on-chemicals

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. 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 LNs 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 are 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 (see *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.

3.1.3 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 ITNs because of the possible repeated dermal exposure of the users of the nets. Inhalation toxicity studies may be of value in the assessment of risks to operators who are subject to potential acute and repeated inhalation exposure.

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 value. 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 also 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 data on dermal absorption of dry insecticides deposited on the skin or incorporated or coated on nets, the higher estimate (concentrated or dilute) of the active ingredient is used (EFSA 2011, 2014).

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.

3.1.4 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 ITNs, 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 a dose–response relationship, no-observed-adverse-effect-level (NOAEL) and lowest-observed-adverse-effect-level (LOAEL)?

3.1.5 Insecticides not recommended for treatment of nets

Compounds meeting the criteria for carcinogenicity, mutagenicity or reproductive toxicity categories 1A and 1B of the *Globally harmonized system on classification and labelling of chemicals* (United Nations, 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 revised 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 net treatment 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.

3.1.6 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, reduce 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).

3.1.7 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. of 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 reference values for long-term low-level residual exposure of ITN users 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 an 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, 2009a). 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 (WHO 2011a, 2011b, 2011c).

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 considered to 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 variability 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 by 50% [2 and 1.58, respectively], and the overall variability factor thus be lowered from the traditional 100 ($4 \times 2.5 \times 3.16 \times 3.16$) to 25 ($2 \times 2.5 \times 1.58 \times 3.16$) (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; JMPR, 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 & Renwick, 2005; Dourson, Knauf & Swartout, 1992; Herman & 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 that may be extra-sensitive to the effects of the compound (e.g. newborns, because of their 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 insecticide-treated net use and maintenancee

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, TSDAC (based on, for example, 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 kgbw-1d-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 use and maintenance of insecticide-treated nets 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 generally 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, net dippers and users of ITNs are also exposed via skin contact and – in case of volatile insecticides – 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.

Regional and national occupational exposure limits (OELs) may be available for public health insecticides. 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. Dipping of ITNs may also be performed by pregnant women. The UFs applied in setting guidelines for ITN users/dippers thus usually need to be significantly larger than those applied in setting OELs.

Acute exposure: Guidance values for acute (24-hour) dietary exposure to agricultural plant protection products have 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 (ARfD)s.

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). Since 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 maintenance of retreatable ITNs, a tolerable systemic dose for acute exposure, TSDAC, 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 net dipping and washing.

For most of the common insecticides used for net treatment, an ARfD from JMPR is available for the derivation of the TSDAC 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 ITNs when no authoritative acute reference dose is available.

3.2 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. These considerations may indicate different scenarios for the following groups of people involved in the use and maintenance of treated nets:

- those sleeping under treated nets;
- those washing treated nets; and
- those involved in the manufacture and distribution of the insecticide treated nets (not further considered here).

Conventional retreatment of nets additionally involves the following groups (dealt with in the Annex):

- those treating nets with insecticide; and
- those who might accidentally ingest concentrated insecticide.

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 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 ITN use and maintenance 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).

It is the aim of this document to provide an estimate of the risks in users of the nets as well as persons washing the nets (adults and children). In the Annex, dipping and washing of conventional nets is discussed.

3.2.1 General parameters for exposure assessment

It should be emphasized that more chemical-specific or case-specific data should always be sought and used when possible.

- Risks 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.
- Adults are assumed to weigh 60 kg. Risks are also estimated for children aged 6 to < 11 years (assumed to weigh 23.9 kg), toddlers aged 12–24 months (10 kg) and infants (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 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).
- The concentration of the active ingredient in the net is calculated from the WHO specification of the net (default variability of the concentration being ± 25%) as 1.25 × nominal concentration of the a.i. mg/kg net × weight of the net kg/m^2.
- 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.

3.2.2 Sleeping under treated nets

The potential routes of exposure that need to be taken into account in risk assessments for those sleeping under treated nets are inhalation, dislodgeable residues from the net being deposited on skin in contact with the net, and, in the case of infants and young children, the additional possibility that the net may be mouthed, chewed or sucked. In the risk assessment scenarios that follow, the examples of an adult, a child aged 6 to < 11 years, a toddler aged 1 to < 2 years and weighing 10 kg, and an infant aged < 12 months and weighing 8 kg are presented. As a conservative estimate, it is assumed that the net is used every night the year around.

Washing experiments have shown that LNs retain a considerable amount of insecticide for a long time; the bulk of the insecticide coated or incorporated in the net is not immediately available for transfer (on the skin, mouth or washing water) but rather is within the netting polymer and only slowly migrates to the surface (e.g. after removal of the surface layer in net washing). The wash-resistance index, as determined with the CIPAC method MT 195 (described at http://cipac.org/index.php/mt-195-wash-resistance-index-of-ln-s), reflects the amount of the insecticide available for transfer in that the amount available is (100–wash-resistance index)%. This is the amount assumed to be transferred to the washing water when the net is washed. The amount actually transferred onto the skin is assumed to be the translodgeable fraction of the surface concentration from a soft surface, the defaults for which are derived from the USEPA standard operating procedure (SOP) (USEPA, 2012). Similarly, the fraction transferred to the mouth is assumed to be the fraction of the surface concentration extracted to saliva (USEPA, 2012). It should be noted that there are considerable uncertainties in these approaches. For the translodgeable fraction, and salivary extraction, actual measured chemical-specific values are likely to considerably enhance the accuracy of the exposure estimate. In this guideline, it is conservatively assumed that the concentration of insecticide in the net is not significantly changed over the time it is used; that is, the exposure resulting from sleeping under the net – whether by inhalation or by the dermal or oral route – is the same as that from an unused or unwashed net.

Exposure from conventionally treated nets is discussed in the Annex.

Inhalation

Many attempts have been made to model the indoor air environment, all of which have shown that the factors which contribute to the composition of the indoor air environment are extremely complex and not readily amenable to mathematical modelling. The model used here thus may only give a very rough estimate of inhalation exposure.

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).

Until now, mostly pyrethroids have been used to impregnate nets; they have low vapour pressures (see *Table 4*). Experimental work on deltamethrin concentrations in the air under nets has shown that inhalation exposure is negligible – only 0.07–2.0% of the exposure which occurs via the oral and dermal routes (Barlow et al., 2001). Studies on occupationally exposed pesticide workers have also shown that inhalation exposure is usually a small percentage of the dermal exposure (Hayes, 1975). Thus, in using pyrethroids, the contribution of inhalation to total body exposure is so small that, in practice, it can be ignored. This is corroborated by the study of Peterson et al. (2011) and the recommendation of the USEPA SOP for residential exposure estimates, dealing with post-application doses from materials impregnated with pesticides (USEPA, 2012). The SOP states that, in most cases, inhalation exposure from impregnated materials is expected to be negligible, since many pesticides that are used in impregnated materials have relatively low vapour pressures. As a result, inhalation exposure is not expected to result in appreciable exposure when compared with dermal and non-dietary ingestion exposure (USEPA, 2012). However, with insecticides other than pyrethroids, it may be relevant to estimate inhalation exposure (*Table 4*). In order to assess the need to evaluate this exposure, the worst case of exposure (a toddler staying 24 hours/day at a saturated vapour pressure concentration) to 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.: the inhalation exposure can be roughly estimated from the equation C_{air} (μg/m^3) = 1.01 x 10^{-3} × SC × VP, where SC = surface concentration in the net (mg/m^2) and VP = vapour pressure at 25 °C (μPa) using standard values for respiratory volume as shown in *Box 1*.[1] This approach taken for vapour would not apply in other situations where aerosols are present (e.g. where insecticides are sprayed rather than incorporated into materials).

[1] In a limited study (Bomann, 1991), 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. Assuming that the room temperature is approximately 25°C, that the airborne concentration of an insecticide is directly proportional to the vapour pressure, evaporation surface area and surface concentration, and inversely proportional to the volume of the evaporation space, the predicted concentration (μg/m^3) of an insecticide will be:

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

In the model standard room, (4 × 4 × 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, 1.01 × 10^{-3} × VP × TC.

Table 4. Vapour pressure of selected pesticides at room temperatures (20–25 °C)[a]

Chemical	Vapour pressure (µPa)
Organochlorines	
DDT	25
Endosulfan	830
Methoxychlor	190
Pyrethroids	
Alpha-cypermethrin	0.17
Cyfluthrin (most volatile isomer)	0.96
Deltamethrin	2.0
Etofenprox	0.8
Lambda-cyhalothrin	0.2
Permethrin	2.5
Organophosphates and carbamates	
Azinphos-methyl	180
Chlorpyrifos	2,500
Chlorpyrifos methyl	5,600
Dichlorvos	1,600,000
Fenitrothion	18,000
Malathion	450
Pirimiphos-methyl	2,000
Bendiocarb	4,600
Carbosulfan	41

a Data taken from The pesticide manual (Worthing, 1991), from IPCS Environmental Health Criteria for the specific substances, or from FAO/WHO specifications.

Skin contact

For anyone sleeping under a treated net, contact between the net and bare skin is to be expected. The quantity of the insecticide transferred to the skin may vary with the type of insecticide, type of net material, shape of the net and humidity. In the case of LNs, it may also vary with the treatment technology (i.e. incorporation or coating). It is assumed that the fraction available for skin contact in an LN can be estimated from the wash-resistance index (WRI) as: 100–WRI%.

USEPA (2012) recommended point estimate for the dislodgeable fraction from carpets is 6%, based on studies on four pyrethroids, chlorpyrifos and piperonylbutoxide. The figures for potential surface area in contact with the net shown in *Table 5* have been estimated using data on skin surface areas of parts of the body adapted from USEPA (2011), assuming that the trunk, hands, arms, lower legs and feet are uncovered and that one-third of their total surface area could be in contact with the net.

BOX 1. Inhalation of insecticide while sleeping under a treated net

Predicted daily systemic dose from inhalation exposure while sleeping under a treated net is:
$SysD_{TWA} = Abs_{Inh} \times C_{air}$ x BV x H/BW µg kg_{bw}^{-1} where:

$SysD_{TWA}$	=	TWA systemic daily dose from inhalation exposure (µg kg_{bw}^{-1})
Abs_{Inh}	=	absorption from the respiratory tract (default, 100%)
C_{air}	=	concentration of insecticide in breathing zone (µg/m^3)[1]
BV	=	breathing volume (m^3/hour)
H	=	average time spent under net each day (hours)
BW	=	body weight (kg) (*Table 3*)

Data on respiratory volumes at rest for adults and children indicate that the following values can be used for BV (USEPA, 2011):

adult	0.29 m^3/h
child (6–< 11 years)	0.27 m^3/h
toddler (1–< 2 years)	0.27 m^3/h
infant (0–< 1 year)	0.18 m^3/h

Average sleeping times are estimated to be: adult, 9 hours; child, 10 hours; toddler, 12 hours, infant (0–< 1 year) 13 hours (USEPA, 2011)

Table 5. Skin surface area potentially in contact with the net (m^2)[a]

	Adult	Child	Toddler	Infant
Trunk	0.190	0.113	0.060	0.051
Hands	0.027	0.014	0.008	0.007
Arms	0.076	0.042	0.021	0.019
Lower legs	0.077	0.036	0.018	0.015
Feet	0.038	0.020	0.010	0.008
Total	0.408	0.225	0.115	0.100

a Assumes one-third of surface area of body part is in contact with the net; adapted from USEPA, 2011, HEEG, 2013a. Calculated from body surface data presented in *Table 3*.

For chemicals that do not have chemical-specific data, USEPA (2012) recommends a screening level point estimate of 0.06 for use in post-application dermal exposure assessments based on studies on 3 pyrethroids, chlorpyrifos and piperonylbutoxide. This, taken to be the default value for the transfer of the insecticide from the net to the sleeper during a night, would be a worst-case estimate since it assumes that 6% of the target dose is dislodgeat ⅓ of their total surface area could be in contact with the net.

If dermal penetration data are available, the percentage of the transferred material that will be absorbed into the body can be calculated. In the absence of penetration data, for the default values, see *Section 3.1.3*.

The potential daily dermal exposure may be calculated as shown in *Box 2*.

BOX 2. Dermal exposure from sleeping under a treated net

$SysD_{TWA} = Abs_D \times Transl \times ESA \times SF \times TC/BW$, where

$SysD_{TWA}$	=	systemic dose from dermal exposure mg kg_{bw}^{-1}
Abs_D	=	dermal absorption from net surface (see *Section 3.1.3*)
Transl	=	translodgeable fraction (default 6%)
ESA	=	exposed skin area m^2 (see *Table 5*)
SF	=	surface fraction of the insecticide (100–wash resistance index%; see *Section 3.2.2*)
TC	=	concentration of the a.i. in the net (mg/m^2 see *Section 3.2.1*)
BW	=	body weight (see *Table 3*)

Oral exposure

Oral exposure may occur from hand-to-mouth transfer and from direct mouthing of the net in the case of infants and toddlers.

Oral exposure via hand-to-mouth transfer can be calculated as shown in *Box 3*. The amount transferred to the hands is estimated from the fraction available on the net surface – as determined from the wash-resistance index – and the translodgeable fraction using soft surfaces (USEPA, 2012) as representing the net. The fraction of hands mouthed is estimated from the USEPA model (2012) as is the salivary extraction. Refined estimates of the amount actually released from LNs may be achieved by determining the release rate from the LN in artificial saliva.

BOX 3. Oral exposure from hand-to-mouth activity

$SysD_{TWA} = Abs_0 \times SE \times Transl \times EHA \times FHM \times SF \times TC / BW$ mg kg_{bw}^{-1}, where

$SysD_{TWA}$	=	systemic dose from oral exposure from hand-to-mouth activity, mg/kg bw
Abs_0	=	oral absorption (default, 100%)
Transl	=	translodgeability (default, 0.06; 75th percentile from carpet (USEPA, 2012)
EHA	=	exposed hand area, 0.008 for toddlers, 0.007 for infants (*Table 5*)
FHM	=	fraction of hand mouthed (default, 0.164; 75th percentile (USEPA, 2012)
SE	=	salivary extraction fraction (default 0.57; 75th percentile) (USEPA, 2012)
SF	=	surface fraction of the insecticide (default, 100–wash resistance index%)
TC	=	concentration of insecticide on the net mg/m^2 (see *Section 3.2.1*)
BW	=	body weight (infant 8 kg, toddler 10 kg; *Table 3*)

Infants and toddlers may also mouth, chew and suck the nets. It is assumed that an area of 14 cm^2 (0.0014 m^2) of the net is in contact with the mouth overnight (75th percentile from USEPA (2011) data) and that the fraction available on the net surface – as determined from the wash-resistance index – will be the target for salivary extraction. Oral exposure via this route can be calculated as shown in *Box 4*.

BOX 4. Oral exposure from direct mouth contact with the net

$SysD_{TWA}$ = $Abs_O \times SE \times NM \times SF \times TC/BW$, where

$SysD_{TWA}$	=	systemic dose from oral exposure from direct net mouthing, mg/kg bw
Abs_O	=	oral absorption (default, 100%)
SE	=	salivary extraction fraction (default 0.57; 75th percentile) (USEPA, 2012)
NM	=	net mouthed, m^2 (default, 0.0014 m^2; 75th percentile) (USEPA, 2012)
SF	=	surface fraction of the insecticide (default, 100–wash resistance index%; see *Section 3.2.2*)
TC	=	concentration of insecticide on the net mg/m^2 (see *Section 3.2.1*)
BW	=	body weight (infant 8 kg, toddler 10 kg; *Table 3*)

Total exposure from all routes while sleeping under a treated net

A worst case for total daily systemic dose of the insecticide while sleeping under a net is calculated from the systemic doses from inhalation, skin contact, oral contact with the net and hand-to-mouth transfer.

3.2.3 Washing of treated nets

It is assumed that both adults and children may carry out the washing of nets. Nets are likely to be washed 20 times over 3 years (WHO, 2009c; WHO, 2009d). The exposure is determined by the volume of the water used in washing, and the rate of release of the insecticide from the treated net. For a net of approximately 15 m^2, the volume of washing fluid is unlikely to be less than 4 litres. The exposure is considered to be acute; thus the appropriate reference point is the TSD_{AC}. However, washing is done by people using the net and thus also contributes to their long-term exposure.

Box 5. Dermal exposure during the washing of nets

It is assumed that the 5 nets of a family are washed at a time; that the volume of water used for washing is 4 litres; that gloves are not worn; and that contaminated skin is not rinsed immediately after the washing of the net.

$SysD_{TWA}$ = $NoW \times NoN \times Abs_D \times VLS \times SF \times TC \times SN / (VolW \times BW \times AT)$

$SysD_{MAX}$ = $NoN \times Abs_D \times VLS \times SF \times TC \times SN / (VolW \times BW)$, where:

$SysD_{TWA}$	=	predicted time-weighted average (TWA) daily systemic dose from washing nets mg/kg bw
$SysD_{MAX}$	=	predicted maximal daily systemic dose from washing 5 nets, mg/kg bw
NoW	=	number of washes per year (default 20 washes/3 years)
NoN	=	number of nets washed per day (default, 5)
Abs_D	=	dermal absorption (see *Section 3.1.3*)
VLS	=	volume of liquid on skin (adults 36.7 mL, children 17.6 mL, consisting of hands, fore arms, ½ of lower legs and ½ of feet covered by a liquid film of 0.1 mm; see *Table 3*)
SF	=	surface fraction of the insecticide = fraction released in a wash (see *Section 3.2.2*)
TC	=	target concentration in the net (mg/m²); see *Section 3.2.1*. (When different parts of the net have different target concentrations, that for the sides of the net should be used.)
SN	=	size of the net m²
VolW	=	volume of washing water (default, 4000 mL)
BW	=	body weight (adult 60 kg, child 23.9 kg; see *Table 3*)
AT	=	averaging time (365 days)

For LNs, the amount released from the net during washing may be estimated from the wash resistance index.

The amount deposited on the skin and absorbed systemically during washing can be calculated as shown in *Box 5*. Washing of nets may also lead to oral exposure through hand-to-mouth transfer. The extent of such exposure may be estimated as shown in *Box 6*.

Box 6. Oral exposure (hand-to-mouth behaviour) during the washing of nets

$SysD_{TWA} = NoW \times NoN \times Abs_0 \times VLH \times SF \times TC \times FHM \times SN/(VolW \times BW \times AV)$

$SysD_{MAX} = NoN \times Abs_0 \times VLH \times SF \times TC \times FHM \times SN/(VolW \times BW)$, where:

$SysD_{TWA}$	=	predicted TWA daily systemic dose
$SysD_{MAX}$	=	predicted maximal daily systemic dose
NoW	=	number of washes per year (default 20 washes/3 years)
NoN	=	number of nets washed per day (default, 5)
Abs_0	=	oral absorption (default 100%)
VLH	=	volume of liquid on hands (mL) (adult 8.2 mL, child 4.3 mL)
SF	=	surface fraction released in a wash = fraction released in a wash; see *Section 3.2.2*)
TC	=	target concentration in the net (mg/m2); see *Section 3.2.1*. (When different parts of the net have different target concentrations, that for the sides of the net should be used.)
FHM	=	fraction of hands actually mouthed default 0.164 (75th percentile) (USEPA, 2012)
SN	=	[maximal actual] size of the net (m^2)
$VolW$	=	volume of washing water (default 4 litres)
BW	=	body weight (kg) (adult, 60 kg, child, 23.9 kg) (*Table 3*)
AT	=	averaging time (365 days)

3.2.4 Treating nets with insecticide

When information is available on the fraction of the mother's dose excreted in 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, 1999) (*Box 7*). The time-weighted average (TWA) for the infant is calculated from the TWA-exposure of the mother, the maximal daily dose of the infant, from the mother's exposure on the day she washes the family's nets.

Box 7. Exposure via breast milk estimated from fraction of dose excreted in milk

$SysD_{TWA} = Fr_{milk} \times Abs_0 \times DoseM_{TWA} \times BW_M \times UF / BW$

$SysD_{MAX} = Fr_{milk} \times Abs_0 \times DoseM_{MAX} \times BW_M \times UF / BW$, where:

$SysD_{TWA}$	=	TWA systemic dose of the breast-fed infant due to the excretion of the pesticide in mother's milk mg/kg body weight per day
$SysD_{MAX}$	=	maximal systemic dose of the breast-fed infant due to the excretion of the pesticide in mother's milk (on the washing day) mg/kg body weight
Fr_{milk}	=	fraction of the dose excreted in milk in an experimental animal
Abs_0	=	oral absorption rate (default, 100%)
$DoseM_{TWA}$	=	TWA dose the mother (mg/kg bw per day)
$DoseM_{MAX}$	=	dose of the mother on the net washing day
BW_M	=	body weight of the mother, 60 kg
UF	=	interspecies kinetic variability factor 100.6 = 3.98
BW	=	body weight kg infant, 8 kg, newborn, 4.2 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 pesticide as follows (*Box 8*).

Concentration of the pesticide in breast milk is estimated from the exposure of the mother at steady state. Body burden = daily dose mg/kg bw × T½ (days)/ln(2) (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 8*). 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 8*).

Box 8. Exposure via breast milk estimated from kinetic properties

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

$SolC$	=	solubility constant; 1.4 for water-soluble and 0.361 for lipid soluble insecticides
$Dose_{Mbw}$	=	daily dose to the mother mg/kg bw
$T½$	=	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; 75th percentile default for a newborn is 640 mL/day (USEPA, 2011), thus with a relative density of milk of 1.03, daily consumption would be 0.66 kg/day
Abs_O	=	fraction absorbed (default is 100%)
BW	=	body weight (infant, 8 kg; newborn 4.2 kg; *Table 3*)

The systemic dose from the exposure through breast milk is added to the infant's dose from sleeping under the net, and the sum is compared with the TSD.

3.3 Risk characterization

The aim of 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 TWA exposure with 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 LNs may be unacceptable. Application of chemical-specific data instead of model defaults may be sought to refine the risk assessment. 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.

3.3.1 Special considerations in relation to insecticide-treated nets

Early warning of undesirable exposures

Information on toxicity may be available from human case reports and from occupational and epidemiological studies, which may indicate the levels of exposure that are known to be toxic for humans and the type of toxicity to be expected. The nature of the first signs of toxicity in humans is important to the risk assessment. It is an advantage if the first signs are easily recognized, benign and reversible on stopping exposure – this will help to avoid excessive exposure. If, however, the first signs of excessive exposure are serious, prolonged or life-threatening, much larger margins of safety may be needed to achieve an acceptable exposure level. With pyrethroids, for example, an early sign of excessive exposure is tingling sensations in the face. This seems to occur at exposure levels below those that cause other types of toxicity, and is reversible on stopping exposure. Persistence of such effects provides a warning sign that overexposure could be occurring and that steps to reduce exposure should be taken. With anticholinesterase exposure, changes in visual acuity or pupil size may indicate overexposure. Such benign, reversible warnings are valuable in preventing overexposure in general use situations and may be taken into account in determining acceptable margins of exposure.

Health and nutritional status of individuals

Under the conditions in which ITNs will be used, consideration may also need to be given to the role of other factors, such as nutrition and intercurrent disease, that may influence toxic reactions to pesticides. Animal studies are normally carried out on healthy, well-nourished animals, which may be more resistant to the toxic effects of a pesticide than individuals who are malnourished, suffer from specific nutritional deficiencies or have infections that might impair liver or renal function. For example, the metabolism of some chemicals depends on adequate folate or glutathione reserves being available for detoxification. The traditional safety margins built into the derivation of acceptable exposure levels would be expected to take account of much of these interindividual differences. Pregnancy is another factor that may need separate consideration. Since the embryo and fetus may be more susceptible than adults and children, special attention should be paid to any potential risks during pregnancy and should be reflected in the data on reproductive toxicity. If no such data are available, no conclusions can be drawn about the safety of exposure during pregnancy.

It is relatively unusual for chemicals to be absorbed through the skin in sufficient amounts to cause death. However, some insecticides have acute dermal LD_{50} values in animals which indicate that mortality has been induced following dermal application (see WHO, 2010). For such substances, it is important to determine whether there may be circumstances in which severe toxicity could be induced as a result of accidental dermal exposure or careless handling. The risk–benefit considerations may well preclude the use of such substances as insecticides for net treatment because of the potential risks to those treating nets.

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 available risk management approaches other than LNs (see http://www.who.int/malaria/areas/vector_control/en/).

4. SUMMARY OF THE MODEL AND A WORKED EXAMPLE

Below is a summary of the generic model together with a worked example on an LN factory-treated with PYR, a pyrethroid.

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 Reviews (WHO IPCS, JMPR, USEPA, PSD, IARC, ATSDR, etc.) on PYR were consulted and a literature search was conducted on MEDLINE and TOXLINE.
1.2 Obtain relevant reviews and key original papers.	1.2 Comprehensive reviews available from IPCS and IARC. Repeat-dose rat dermal study available from manufacturer. Key human occupational and poisoning 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, most via oral route, with some inhalation and dermal studies. Most conducted to acceptable standards with adequate dose–response data.
1.5 If database is adequate, identify critical toxic effect(s).	1.5 In humans, first toxic symptom is facial paraesthesia, reversible on cessation of exposure. Critical toxic effect in animals is neurotoxicity.
1.6 If the insecticide is genotoxic or extremely acutely toxic via dermal or oral routes, consider whether it is worth proceeding with risk assessment.	1.6 PYR is not genotoxic and has low acute toxicity. 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 human occupational studies (for paraesthesia), 1-year dog dietary study, and 90-day rat gavage study (for neurotoxicity).
1.8 Identify critical NOAEL(s) from pivotal studies for acute exposure and for longer-term (repeat-dose) exposure.	1.8 Critical NOAELs for PYR: – acute oral exposure human: 1.75 g/day. – 90-day gavage, rat, and 1-year dietary, dog: 1 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 adequate to allow setting of TSDs for short- and long-term exposure.
1.10 Where reputable bodies have set appropriate guidelines, use these to derive TSDs for ITN scenarios.	1.10 An ADI of 0–0.01 mg kg_{bw}^{-1} was set by JMPR in 1982 and most recently confirmed in 2000. JMPR has also set an ARfD of 0.05 mg kg_{bw}^{-1} Oral absorption (Abs_{oral}) = 75%

Generic risk assessment model	Worked example
2. Exposure assessment **Aim: To estimate exposure via dermal, oral and inhalation routes during use and washing of nets.**	
2.1 Inhalation, dermal, and oral exposure from sleeping under treated nets	
a) Inhalation	
If inhalation could be significant (high vapour pressure and toxicity) add amount for inhalation, using formula in *Box 1*, and assuming 100% of amount inhaled is absorbed systemically.	PYR has vapour pressure of 3.9 x 10^{-6}Pa and molecular mass 505.2. Thus worst case systemic dose is 0.328 x 505 x 3.9 x 10^{-6} mg/kg bw = 0.6 µg/kg, which is 6% of the TSD. Thus inhalation is negligible and can be ignored.
b) Dermal	
$SysD_{TWA}$ = Abs_D × *Transl* × *ESA* × *SF* × *TC/BW* (mg kg_{bw}^{-1}) (*Box 2*) Abs_D: dermal absorption; the default for pyrethroids, 10% is used. *Transl*: 75th percentile translodgeability for PYR from carpet has been shown to be 2%; *Transl* = 2%ESA: skin surface in contact with the net is 0.408, 0.225, 0.115 and 0.100 m^2 in adults, children, toddlers and infants (*Table 5*) *SF*: wash resistance index for PYR is 93.5%; thus the surface fraction *SF* = 6.5% *TC*: nominal concentration on the net = 55.5 mg/m^2; the specification uncertainty, ± 25%. Thus the *TC* = 69.4 mg/m^2.	Predicted TWA systemic dose from dermal contact is for adults: 0.1 × 0.02 × 0.408 × 0.065 × 69.4/60 mg $kg_{bw}^{-1}d^{-1}$ **= 0.06 µg $kg_{bw}^{-1}d^{-1}$** For a 23.9-kg child: 0.1 × 0.02 × 0.225 × 0.065 × 69.4/23.9 mg $kg_{bw}^{-1}d^{-1}$ **= 0.08 µg $kg_{bw}^{-1}d^{-1}$** For a 10-kg toddler: 0.1 × 0.02 × 0.115 × 0.065 × 69.4/10 mg $kg_{bw}^{-1}d^{-1}$ **= 0.10 µg $kg_{bw}^{-1}d^{-1}$** For an 8-kg infant: 0.1 × 0.02 × 0.100 × 0.065 × 69.4/8 mg $kg_{bw}^{-1}d^{-1}$ **= 0.11 µg $kg_{bw}^{-1}d^{-1}$**
c) Oral, hand-to-mouth	
$SysD_{TWA}$ = Abs_O × *SE* × *Transl* × *EHA* × *FHM* × *SF* × *TC* / *BW* mg kg_{bw}^{-1} (see *Box 3*) Abs_O for PYR is 75% *SE*: salivary extraction, default value is used SE = 0.57 *Transl*: 75th percentile translodgeability for PYR from carpet has been shown to be 2%; Transl = 2% *EHA*: exposed hand area, EHA, 0.008 for a toddler, 0.007 for an infant *FHM*: fraction of hand mouthed, FHM = 0.164 *SF*: surface fraction. Wash resistance index for PYR is 93.5%; thus the surface fraction SF = 0.065 *TC*: target concentration on the net = 55.5 mg/m^2; the specification uncertainty, ± 25%. Thus TC = 69.4 mg/m^2 *BW*: body weight for a toddler, 10 kg and for an infant, 8 kg	Predicted systemic dose is: For toddlers: 0.75 × 0.57 × 0.02 × 0.008 × 0.164 × 0.065 × 69.4/10mg $kg_{bw}^{-1}d^{-1}$ **=0.005 µg $kg_{bw}^{-1}d^{-1}$** For infants: 0.75 × 0.57 × 0.02 × 0.007 × 0.164 × 0.065 × 69.4/8mg $kg_{bw}^{-1}d^{-1}$ **=0.006 µg $kg_{bw}^{-1}d^{-1}$**
d) Oral, direct mouth contact with net	
$SysD_{TWA}$ = Abs_O × *SE* × *NM* × *SF* × *TC/BW* mg $kg_{bw}^{-1}d^{-1}$ (see *Box 4*) Abs_O: oral absorption for PYR is 75% *SE*: salivary extraction, default value is used *SE* = 0.57NM: net mouthed, default *NM*= 0.0014 m^2 *SF*: surface fraction. Wash resistance index for PYR is 93.5%; thus the surface fraction SF = 0.065 *TC*: target concentration on the net = 55.5 mg/m^2; the specification uncertainty, ± 25%. Thus TC = 69.4 mg/m^2 *BW*: body weight for a toddler, 10 kg and for an infant, 8 kg	Predicted systemic dose is: For toddlers 0.75 × 0.57 × 0.0014× 0.065 × 69.4/10 mg $kg_{bw}^{-1}d^{-1}$ **= 0.27 µg $kg_{bw}^{-1}d^{-1}$** For infants 0.75 × 0.57 × 0.0014 × 0.065 × 69.4/8 mg $kg_{bw}^{-1}d^{-1}$ **= 0.34 µg $kg_{bw}^{-1}d^{-1}$**

Generic risk assessment model	Worked example
e) Total dose from sleeping under the net	
Sum of systemic dose from inhalation, dermal and oral exposure	Systemic dose for an adult is **0.06 µg $kg_{bw}^{-1}d^{-1}$** Systemic dose for a child is **0.08 µg $kg_{bw}^{-1}d^{-1}$** Systemic dose for a toddler is 0.10 + 0.005 + 0.27= **0.38 µg $kg_{bw}^{-1}d^{-1}$** Systemic dose for an infant is 0.11 + 0.006 + 0.34 = **0.46 µg $kg_{bw}^{-1}d^{-1}$**
2.2 Systemic exposure during washing of nets	
a) Dermal exposure during net washing	
$SysD_{TWA} = NoW \times NoN \times Abs_D \times VLS \times SF \times TC \times SN / (VolW \times BW \times AT)$ (mg kg_{bw}^{-1}) (*Box 5*) $SysD_{MAX} = NoN \times Abs_D \times VLS \times SF \times TC \times SN / (VolW \times BW)$ (mg kg_{bw}^{-1}), where: *NoW* = no. of washes per net per year; 20/3 *NoN* = no. of nets washed/day; 5 Abs_D = dermal absorption; 10% *VLS* = volume of liquid on skin (adult 36.7 mL, child 17.6 mL *SF* = surface fraction. Wash resistance index for PYR is 93.5%; thus the surface fraction SF = 0.065 *TC* = target concentration on the net = 55.5 mg/m^2; the specification uncertainty, ± 25%. Thus TC = 69.4 mg/m^2. *SN* = size of net = 15 m^2 *VolW* = volume of washing water; 4000 mL *BW* = body weight 60 kg for an adult, 23.9 kg for a child *AT* = averaging time (365 days)	The TWA systemic dose is: For an adult 20 × 5 × 0.1 × 36.6 × 0.065 × 69.4 × 15 / (3 × 4000 × 60 × 365) = 0.09 µg $kg_{bw}^{-1}d^{-1}$ For a child 20 × 5 × 0.1 × 17.6 × 0.065 × 69.4 × 15 / (3 × 4000 × 23.9 × 365) = 0.11 µg $kg_{bw}^{-1}d^{-1}$ The maximal daily dose is: For an adult 5 × 0.1 × 36.6 × 0.065 × 69.4 × 15 / (4000 × 60) = 5.16 µg kg_{bw}^{-1} For a child 5 × 0.1 × 17.6 × 0.065 × 69.4 × 15 / (4000 × 23.9) = 6.23 µg kg_{bw}^{-1}
b) Oral exposure (hand-to-mouth) during net washing	
The TWA systemic dose is (*Box 6*): $SysD_{TWA} = NoW \times NoN \times Abs_O \times VLH \times SF \times TC \times FHM \times SN / (VolW \times BW \times AT)$ (mg kg_{bw}^{-1}) $SysD_{MAX} = NoN \times Abs_O \times VLH \times SF \times TC \times FHM \times SN / (VolW \times BW)$ (mg kg_{bw}^{-1}) where: *NoW* = no. of washes per net per year; 20 washes/3 years *NoN* = no. of nets washed / d; 5 Abs_O = oral absorption; 75% *VLH* = volume of liquid on hands (adults 8.2 mL, children 4.3 mL) *SF* = surface fraction. Wash resistance index for PYR is 93.5%; thus the surface fraction SF = 0.065 *TC* = target concentration on the net = 55.5 mg/m^2; the specification uncertainty, ± 25%. Thus TC = 69.4 mg/m^2 *FHM* = fraction of hands actually mouthed default 0.164 *SN* = size of net = 15 m^2 *VolW* = volume of washing water; 4000 mL *BW* = body weight 60 kg for an adult, 23.9 kg for a child *AT* = averaging time (365 days)	The TWA systemic dose is: For an adult: 20 × 5 × 0.75 × 8.2 × 0.065 × 69.4 × 0.164 × 15 / (3 × 4000 × 60 ×365) = **0.03 µg $kg_{bw}^{-1}d^{-1}$** For a child 20 × 5 × 0.75 × 4.3 × 0.065 × 69.4 × 0.164 × 15 / (3 × 4000 × 23.9 ×365) = **0.03 µg $kg_{bw}^{-1}d^{-1}$** The maximal daily systemic dose is: For an adult 5 × 0.75 × 8.2 × 0.065 × 69.4 × 0.164 × 15 / (4000 × 60) = **1.42 µg $kg_{bw}^{-1}d^{-1}$** For a child 5 × 0.75 × 4.3 × 0.065 × 69.4 × 0.164 × 15 / (4000 × 23.9) = **1.87 µg $kg_{bw}^{-1}d^{-1}$**

Generic risk assessment model	Worked example
c) Total dose from net washing	
Sum of dermal and oral (hand-to-mouth) exposure	The TWA systemic dose is: For an adult = 0.09 + 0.03 = **0.12 µg $kg_{bw}^{-1}d^{-1}$** For a child = 0.11 + 0.03 = **0.14 µg $kg_{bw}^{-1}d^{-1}$** The maximal daily systemic dose is: For an adult = 5.16 + 1.42 = **6.58 µg $kg_{bw}^{-1}d^{-1}$** For a child = 6.23 + 1.87 = **8.10 µg $kg_{bw}^{-1}d^{-1}$**
2.3 Exposure via breast milk Total dose from mother's milk	
$SysD_{TWA} = Fr_{milk} \times Abs_O \times DoseM_{TWA} \times BW_M \times UF / BW_I$ mg/kg body weight $SysD_{MAX} = Fr_{milk} \times Abs_O \times DoseM_{MAX} \times BW_M \times UF / BW_I$ mg/kg body weight (*Box 7*) FR_{milk} = fraction in goat's milk of dose to the dam = 0.5% Abs_O = oral absorption for PYR = 75% $DoseM_{TWA}$ = the TWA dose of the mother from sleeping under the net is 0.06, that from washing the net 0.12 µg $kg_{bw}^{-1}d^{-1}$; thus the TWA $Dose_M$ = 0.18 µg $kg_{bw}^{-1}d^{-1}$ $Dose_{MMAX}$ = the maximal daily dose of the mother from sleeping under the net is 0.06, that from washing the net, 6.59 µg $kg_{bw}^{-1}d^{-1}$; thus the maximal daily $DoseM_{MAX}$ = 6.65 µg kg_{bw}^{-1} BW_M = body weight of the mother 60 kg UF = 100.6 = 3.98 BWi 8 kg for the infant, 4.2 kg for the newborn	Newborn 0.005 × 0.75 × 0.18 × 60 × 3.98 / 4.2 = **0.04 µg $kg_{bw}^{-1}d^{-1}$** Infant 0.005 × 0.75 × 0.18 × 60 × 3.98 / 8 = **0.02 µg $kg_{bw}^{-1}d^{-1}$** Total maximal daily dose from mother's milk Newborn 0.005 × 0.75 × 6.65 × 60 × 3.98 / 4.2 = **1.42 µg kg_{bw}^{-1}** Infant 0.005 × 0.75 × 6.65 × 60 × 3.98 / 8 = **0.74 µg kg_{bw}^{-1}**
3. Risk characterization **Aim: To compare each of the average daily**	
systemic dose estimates obtained in section 2 for each of the scenarios: with the tolerable systemic dose (TSD) and the highest daily dose (a person dipping and washing a net and sleeping under the net) with the TSD_{AC}.	TSD = 7.5 µg $kg_{bw}^{-1}d^{-1}$ and TSD_{AC} = 37.5 µg kg_{bw}^{-1}
3.1 Sleeping under net	
Total systemic dose (inhalation, dermal, oral) is compared with the long-term TSD and acute TSD_{AC}.	TSD for long-term exposure, 7.5 µg $kg_{bw}^{-1}d^{-1}$ is applied. Total systemic dose: adult: 0.06 µg $kg_{bw}^{-1}d^{-1}1$ child: 0.08 µg $kg_{bw}^{-1}d^{-1}$ toddler: 0.38 µg $kg_{bw}^{-1}d^{-1}$ infant: 0.46 µg $kg_{bw}^{-1}d^{-1}$ The contribution of exposure from mother's milk to the TWA exposure of a newborn is ≤ 0.04 µg $kg_{bw}^{-1}d^{-1}$, that to the maximal exposure of the newborn (on the day of net washing), 1.4 µg/kg bw. Systemic doses are all ≤ 10% of the relevant TSD for adults and children of different ages, so can be considered acceptable.

Generic risk assessment model	Worked example
3.2 Exposure from sleeping under the net and net washing	
The TWA systemic dose from washing the net (adult and child) is added to the dose from sleeping under the net. *Acute toxicity from washing of a net* Daily systemic dose on the day of net washing (sleeping under the net + washing) is compared with the TSD_{AC}.	The TWA daily systemic dose is: For an adult 0.06 + 0.12 = **0.18 µg $kg_{bw}^{-1}d^{-1}$**, For a child 0.08 + 0.14 = **0.22 µg $kg_{bw}^{-1}d^{-1}$**. The average daily systemic dose for an adult and child washing the nets and sleeping under the nets is < 4% of the TSD of 7.5 µg $kg_{bw}^{-1}d^{-1}$. The maximal daily systemic dose is: For an adult 0.06 + 6.58 = **6.64 µg kg_{bw}^{-1}** For a child 0.08 + 8.10 = **8.18 µg kg_{bw}^{-1}** and thus ≤ 22% TSD_{AC} of 37.5 µg kg_{bw}^{-1}.
If the systemic dose is below the relevant TSD, it can be reasonably assumed that the conditions for exposure are without appreciable risk to human health.	Systemic dose is below the relevant TSD and TSD_{AC}. Systemic doses from sleeping under the net and from washing the net do not involve unacceptable long-term or acute risks.

ITN, insecticide-treated net – either conventionally treated and retreated net or long-lasting insecticidal net (LN); LOAEL, lowest-observed adverse effect level; NOAEL, no-observed adverse effect level; TSD, tolerable systemic dose.

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6. ANNEX : RISK ASSESSMENT OF THE CONVENTIONAL TREATMENT OF NETS WITH INSECTICIDES

The insecticide-treated nets (ITNs) are nets treated manually by dipping them in aqueous suspension containing an insecticide that coats the netting fibre upon drying. ITNs loose the insecticide upon repeated washing in routine use and require to be retreated to restore their biological efficacy. Unlike the factory treatment of LNs, periodical manual washing and retreatment of nets pose risks to the net users. Therefore, a separate risk assessment is presented here for the ITNs. Furthermore, differences in exposure during use and washing of the conventionally treated nets, and LNs, are pointed out here. This exposure scenario, as detailed below, is limited to conventional treatment of nets in households and by public health programme personnel.

6.1 Treating nets with insecticide

6.1.1 Methods of net treatment

Two methods are currently available for treatment of nets:

- "Do-it-yourself" net treatment kits are available for home use. The insecticide may be supplied in liquid, sachet or tablet form to be suspended in water for net treatment. The treated nets (i.e. ITNs) are then dried and used.
- A central service may be run by trained personnel. Net owners can bring their nets for treatment or retreatment, thus reducing the risks of exposure of untrained members of the public.

This report considers primarily the exposures likely to be associated with "do-it-yourself" home-based net treatment, since it is here that the worst-case exposure scenarios are likely to arise. An estimation of exposure is also presented for a central dipping service, which is more amenable to control, although the larger amounts of insecticide used will necessitate careful control programmes to minimize exposure, both of production personnel, who may be exposed daily, and of the environment.

In order to estimate the exposure of those treating nets with insecticide, it is important to know the proposed formulation of the insecticide to be used, the nature of its packaging and the frequency of application at the outset, all of which factors influence the degree of exposure to the insecticide.

Instructions for net treatments should give clear information on the amount of insecticide formulation to be used for each net and the volume of water in which it should be dissolved or dispersed. If there is no direct experimental evidence relating to levels of exposure, assumptions must be made about the likely volumes of powder or liquid concentrate formulation and of dilute solutions or suspensions that will get onto the skin and be available for absorption, the duration of contact, and the degree of skin penetration of the insecticide. Potential for oral and inhalation exposure during dipping of nets must also be considered. This information will allow estimation of the levels of exposure that may be expected during the different phases of production of ITNs each time they are treated.

6.1.2 Variability in contamination/exposure

Studies on pesticide operators have shown that there may be huge variations in the extent of skin contamination during different parts of the work cycle. For example, when working with a liquid concentrate formulation before dilution, one small drop of concentrate on the skin may cause exposure exceeding the total resulting from all processes that involve diluted material (e.g. spraying, waste disposal). Moreover, workers differ significantly in the care they take when working, so that exposure can vary by orders of magnitude between workers. Thus, for each exposure scenario, there will be a distribution of exposures within a population, and attention should be paid to the extent of variation that may be expected between individuals exposed to the same scenario. The use of any personal protective equipment would also have an influence on exposures.

6.2 Exposure during "do-it-yourself" home-based net treatment

The following factors should be considered in assessing the likely exposure scenarios during home-based treatment of nets:

- who will do it;
- how often they do it;
- whether training/instruction is given;
- nature of the insecticide formulation supplied and its packaging;
- method and volume of dissolution or dispersion;
- whether protective clothing is used (it may be that only gloves will be available);
- whether contaminated protective clothing (e.g. gloves) is reused;
- extent of skin contamination during dipping, hanging out to dry, and disposal of waste insecticide;
- extent of absorption via the skin;
- additional direct exposure via the oral route; and
- additional direct exposure via inhalation.

Who will do it. Both adults – including pregnant women – and children may be involved in dipping nets. Worst-case exposure scenarios are likely to involve children: they may be untrained and less able than adults to follow written or pictorial instructions, and they are of lower body weight than adults, with a greater surface area per kg body weight, resulting in greater exposure on a body weight basis from exposure of the same proportion of the skin surface. Separate exposure estimates are therefore needed for adults and children.

How often. Estimates for the frequency with which nets need to be retreated vary. Ideally, the retention characteristics of the insecticide under consideration should be known and used to determine the retreatment schedule. However, some studies on nets treated with pyrethroids at home or by a central service show that insecticidal activity may be lost in as little as 1–3 months when nets are washed monthly, or after 3 months of household use including two washes (Bhatt et al., 2005; USAID, 2002). Other studies on pyrethroids show little or no decline in insecticidal activity after five washes or 6–7 months of domestic use (Maxwell et al., 1999; Curtis, personal communication). Thus, it could be assumed that home-based retreatment of nets may take place at 3-monthly intervals.

Training or instruction. Under the guideline scenario, training or instruction (verbal, written, and/or pictorial) would be available and followed. For a lax standard scenario, however, it should be assumed that no initial training is available and that any precautionary instructions supplied (e.g. to wear gloves or to pour liquids carefully to avoid splashes) are not necessarily followed.

Nature of the insecticide formulation supplied and its packaging. The insecticide as supplied by the manufacturer may be in the form of liquid concentrate, powder or a solid tablet. Considering the likelihood of operator exposure, a solid tablet is generally the safest formulation; the least safe is generally liquid concentrate, because splashing of concentrate onto skin deposits the active insecticide in a form that may be easily absorbed. Powder may pose an intermediate risk because of the possibility of inhalation.

Similarly, the size and design of the packaging/container in which the formulation is supplied will influence the likelihood of exposure. Pouring a small amount of liquid concentrate from a large-volume container is likely to result in more skin contamination from splashes (and accidents) than if the required amount of concentrate for treatment of a net is supplied in a small, treatment-sized container. Similarly, powder supplied in water-soluble, treatment-sized sachets is likely to result in less exposure than taking a quantity of powder from a larger container. Thus each type of formulation needs a different exposure scenario, which takes account of the type of packaging in which it is supplied.

For liquid concentrates, *Table A1* gives nominal values for the volume of hand contamination caused by emptying containers of liquid concentrate of different volumes. The values are derived from test data using containers of the appropriate design and are the 75th percentile value from pouring tests on each type of container (Pesticides Safety Directorate, 2007). Neck aperture is a critical design feature and *Table A1* shows that the volume of hand contamination is lower when wide-necked containers are used.

Table A1. Values for hand contamination from emptying containers of different volumes and designs[a]

Volume of container	Neck aperture	Contamination of hands (mL/ operation)
1 litre	Any	0.01
2 litres	Any	0.01
5 litres	Narrow	0.2
5 litres	45 mm or 63 mm	0.01
10 litres	Narrow	0.5
10 litres	45 mm	0.1
10 litres	63 mm	0.05
20 litres	Narrow	0.5
20 litres	63 mm	0.05

a Source: PSD, 2007.

Method and volume of dilution or dispersion. The required target dose, i.e. the concentration of the insecticide per unit area of the freshly-treated net, determines the quantity of insecticide in the formulation supplied for dilution and the recommended dilution volume.

This information must be factored into the exposure scenario and should be available from manufacturers or from those conducting field trials; it depends on the method used to dilute the formulation, which will also influence the extent of possible operator contamination. Variables include the type of container used for dilution (bucket, shallow basin), the way in which the formulation is added to the water, and the method used for mixing (e.g. stirring with the (un)gloved hand or with a stick), all of which may influence the degree of splashing and amount of liquid deposited on the skin.

Use of protective clothing. Gloves are likely to be supplied. In the guideline scenario, they are used (see *Box A3* for default contamination values). However, for a lax standard scenario it is assumed that gloves are not used (see *Box A4*). It is unlikely that any other type of protective clothing (e.g. face protection or coveralls) will be used. It should also be borne in mind that, in a hot climate, the skin of the arms and legs is less likely to be protected by normal clothing than is the case in cooler climates.

Reuse of contaminated protective clothing. If gloves are to be reused, they should be washed at the end of the operation while still on the hands (guideline scenario), but it cannot be assumed that this will be done (lax standard scenario). Gloves may also be removed and put on again during the same operation. Both scenarios are likely to result in higher contamination of operators' hands than use of new gloves or gloves previously unused for insecticide treatments.

6.2.1 Dermal exposure during preparation of the dipping solution, dipping, hanging out to dry, and disposal of waste insecticide

Preparation of dipping solutions

As a default (USEPA, 2012), exposure to the formulation from the preparation of the dipping solution is estimated to be 9.7 mg/kg of handled active ingredient for wettable powders (WP), 0.07 mg/kg for water dispersible granules (WG), and 0.04 mg/kg a.i. (active ingredient) for water soluble bags. For liquid formulations, the extent of hand contamination may be estimated from the values presented in *Table A1*. Preparation of the dipping solution from tablets is considered not to cause exposure. Exposure from the preparation of the dipping solution (*Box A1*, *Box A2*) should be added to the exposure calculated below in *Boxes A3*, *A4* and *A5*.

BOX A1. Dermal exposure from preparation of the dipping solution, solid formulations

$SysD_{TWA} = UE_{solid} \times ML \times PPE \times Abs_D \times EF / (BW \times AT)$

$SysD_{MAX} = UE_{solid} \times ML \times PPE \times Abs_D / BW,$ where:

$SysD_{TWA}$	=	systemic TWA dose from the preparation of the dipping solution, mg/kg bw per day
$SysD_{MAX}$	=	maximal daily systemic dose from the preparation of the dipping solution, mg/kg bw
UE_{solid}	=	unit exposure for solid formulations, mg/kg active ingredient handled. Default 9.7 for WP, 0.07 for WG, 0.04 for WSB, 0 for dose tablets
ML	=	amount of insecticide active ingredient mixed and loaded per day (kg) (5 nets × amount a.i./net)
PPE	=	PPE efficacy; guideline scenario: 0.1, lax standard scenario, 1.0)
Abs_D	=	dermal absorption, see *Section 3.1.3*
EF	=	exposure frequency (4 times/year)
BW	=	body weight (60 kg for an adult, 23.9 kg for a child; (*Table 3*)
AT	=	averaging time (365 days)

Dipping, wringing, hanging to dry of the net

Deposition of dilute insecticide on the skin will occur during dipping of the net, wringing it out, and hanging it out to dry. Net materials (cotton, or polyester or other synthetic fibre) vary in their absorbency. Some dipping operations recommend that the net is turned in the container until all the liquid is absorbed, which will reduce the extent of skin contamination from drips when nets are hung outside to dry.

In the absence of actual measurements, default values must be used to estimate the extent of skin contamination during dipping and drying of the nets. This is achieved by estimating volume of solution/suspension contaminating the skin. Examples of scenarios at either end of the likely exposure spectrum are given below – guideline scenario in *Box A3* and lax standard scenario in *Box A4*.

BOX A2. Dermal exposure from preparation of the dipping solution, liquid formulations

$SysD_{TWA}$ = $UEL_{liq} \times PPE \times Abs_D \times EF / (BW \times AT)$

$SysD_{MAX}$ = $UEL_{liq} \times PPE \times Abs_D / BW$, where:

$SysD_{TWA}$	=	systemic TWA dose from the preparation of the dipping solution, mg/kg bw per day
$SysD_{MAX}$	=	maximal daily systemic dose from the preparation of the dipping solution, mg/kg bw
UEL_{liq}	=	Unit exposure for liquid formulations (see *Table A1*) × number of daily operations (5 nets treated per day)
PPE	=	PPE efficacy; guideline scenario: 0.1, lax standard scenario, 1.0)
Abs_D	=	dermal absorption, see *Section 3.1.3*
EF	=	exposure frequency (4 times/year)
BW	=	body weight (60 kg for an adult, 23.9 kg for a child; (*Table 3*)
AT	=	averaging time (365 days)

In the guideline scenario, it is assumed that:

- Hands only are exposed and gloves are worn, used once, and discarded; an overall hand protection factor by gloves of the hands is 90%.
- The film thickness of the liquid on hands is 0.1 mm; the surface area contaminated is as given in *Table 3*.
- The solution/suspension is made up and the nets are dipped and dried in accordance with any instructions provided with the dipping kit.
- The face is not touched by contaminated gloves, and there is thus no hand-to-mouth transfer.
- Any left-over liquid is disposed of safely, without splashing onto skin.
- Hands and any contaminated clothing are washed thoroughly when dipping is finished.

The systemic dose from the insecticide deposited on the skin can be calculated as shown in *Box A3*.

In the lax standard scenario, it is assumed that:

- No gloves are worn.
- The solution is made up by stirring with an ungloved hand, and the nets are dipped and dried without reference to instructions provided with the dipping kit.
- The face may be touched by contaminated hands so that hand-to-mouth transfer is possible.
- There is splashing onto the skin (e.g. legs and feet) during disposal of used solution.
- Hands and any contaminated clothing are not washed when dipping is finished.

The amount deposited on the skin can be calculated as shown in *Box A4*.

BOX A3. Dermal exposure during the dipping of nets (guideline scenario)

It is assumed that gloves give 90% protection against exposure of the hands, i.e. the volume of the liquid on the hands of an adult wearing gloves is 0.82 mL, and that of a child wearing gloves is 0.43 mL (see *Table 3*).

$SysD_{TWA}$ = $NoD \times Abs_D \times VLH \times C_{dip}/(BW \times AT)$ mg $kgbw^{-1}$ per d

$SysD_{MAX}$ = $NoDD \times Abs_D \times VLH \times C_{dip}/BW$, where:

$SysD_{TWA}$ = predicted TWA daily dose from net dipping (mg kg_{bw}^{-1} per d)

$SysD_{MAX}$ = predicted maximal daily dose from a dipping (mg kg_{bw}^{-1})

NoD = number of dippings per year (default 5 nets, 4 times a year = 20)

$NoDD$ = number of dippings per day (default 5 nets)

Abs_D = dermal absorption (see *Section 3.1.3*)

VLH = volume of dipping solution on the hands (adult 0.82 mL, child 0.43 mL)

C_{dip} = concentration of insecticide in the dipping solution (mg/mL; from product label and appropriate dilution)

BW = body weight (adults 60 kg, children 23.9 kg) (*Table 3*)

AT = averaging time (365 days)

6.2.2 Oral exposure

Direct exposure via the oral route would be insignificant in the guideline scenario, but the possibility of hand-to-mouth transfer of insecticide should be borne in mind in the lax standard scenario. Assuming a fraction of hand mouthed (16.4%) and salivary extraction (57%) (USEPA, 2012) of the amount of insecticide on the hands (8.2 mL), and default dermal (10%) and gastrointestinal (100%) absorption for pyrethroids, the hand-to-mouth transfer would add approximately 15% to the dose absorbed percutaneously. For products with a low dermal absorption, the contribution of hand-to-mouth transfer to the total exposure may be very significant (*Box A5*).

BOX A4. Dermal exposure during the dipping of nets (lax standard scenario)

It is assumed that: liquid film thickness on the skin is 0.1 mm; contaminated surface area of skin comprises hands, forearms, ½ of lower legs and ½ of feet (see *Table 3*).

$SysD_{TWA}$ = $NoD \times Abs_D \times VLS \times C_{dip}/(BW \times AT)$

$SysD_{MAX}$ = $NoDD \times Abs_D \times VLS \times C_{dip}/BW$, where:

$SysD_{TWA}$ = predicted TWA daily systemic dose from dipping (mg kg_{bw}^{-1})

$SysD_{MAX}$ = predicted acute dose from dipping (mg kg_{bw}^{-1})

NoD = number of dippings per year (default 5 nets, 4 times a year = 20)

$NoDD$ = number of dippings per day (default 5 nets)

Abs_D = dermal absorption (see *Section 3.1.3*)

VLS = volume of dipping solution on the skin (adult 36.6 mL, child 17.6 mL)

C_{dip} = concentration of insecticide in the dipping solution (mg/mL; from product label and appropriate dilution)

BW = body weight (adults 60 kg, children 23.9 kg) (*Table 3*)

AT = averaging time (365 days)

BOX A5. Oral exposure from hand-to-mouth transfer during dipping (lax standard scenario)

$SysD_{TWA}$ = $NoD \times Abs_0 \times VLH \times FHM \times C_{dip}/(BW \times AT)$

$SysD_{MAX}$ = $NoDD \times Abs_0 \times VLH \times FHM \times C_{dip}/BW$ where:

$SysD_{TWA}$	=	predicted TWA daily dose from a dipping (mg kg_{bw}^{-1})
$SysD_{MAX}$	=	predicted maximal daily dose from a dipping (mg kg_{bw}^{-1})
NoD	=	number of dippings per year (default 5 nets, 4 times a year = 20)
NoDD	=	number of dippings per day (default 5 nets)
Abs_0	=	oral absorption (default 100%)
VLH	=	volume of liquid on hands (adult 8.2 mL, child 4.3 mL; (*Table 3*)
FHM	=	Fraction hand mouthed (default 0.164)
C_{dip}	=	concentration of the insecticide in the dipping solution (from product label)
BW	=	body weight (adults 60 kg, children 23.9 kg)
AT	=	averaging time (365 days)

6.2.3 Exposure from sleeping under the net and from washing of the net

Estimates for how quickly the insecticide washes out from conventional ITNs vary. At worst, the insecticide may wash out over after three monthly washes[1], i.e. the washing fluid contains one-third of the amount of insecticide originally in the net. Thus the formulas developed in the main text for dermal, and oral exposures (hand-to-mouth and direct mouthing) when sleeping under the net, and from washing the net can be applied noting that the default surface fraction of the insecticide (SF) is 33%. It is likely that most net treatments will be conducted in the open air rather than indoors. In these circumstances, since most insecticides are of low volatility, exposure via inhalation has generally been shown to be negligible and need not be taken into account. If net treatments are carried out indoors in unventilated or poorly ventilated areas, additional exposure via inhalation may need to be estimated, depending on the vapour pressure of the insecticide. Insecticides with vapour pressures above 50 µPa (see *Section 3.2.2*) may need this kind of evaluation. Default respiration rates for adults and children are given in *Table 3*.

6.3 Exposure in professional net dipping

Net dipping may be performed centrally by professional staff, in which case it may be assumed that the dipping guideline and label instructions are complied with (guideline exposure scenario). An estimation of the exposure of professional net dippers is presented in *Box A6*.

[1] Duffield LZ, Hordle A (1997). Comparative evaluation of K-Othrine water dispersible tablets and K-Othrine Moustiquaire 1% SC treated bed nets against *Culex quinquefasciatus* and *Anopheles arabiensis*. Berkhamsted (UK): AgrEvo (document A92496, unpublished study made available to authors by AgrEvo, Frankfurt am Main, Germany).

BOX A6. Exposure during professional dipping of nets (guideline scenario)

It is assumed that:

- gloves give 90% protection against exposure of the hands (*Table 3*);
- in a centralized ITN retreatment scheme, a professional dipper treats 20 nets/day on 20 days during each of two seasons/year; and
- only adults are employed in net retreatment.

$SysD_{TWA} = NoD \times Abs_D \times VLH \times PPE \times C_{dip}/(BW \times AT)$

$SysD_{MAX} = NoDD \times Abs_D \times VLH \times PPE \times C_{dip}/BW$, where:

$SysD_{TWA}$	=	predicted TWA daily dose from net dipping (mg kg_{bw}^{-1})
$SysD_{MAX}$	=	predicted acute dose from a dipping (mg kg_{bw}^{-1})
NoD	=	number of dippings per year (default 20 × 20 × 2 = 800)
$NoDD$	=	number of dippings per day (default 20)
Abs_D	=	dermal absorption (see *Section 3.1.3*)
VLH	=	volume of dipping solution on the hands (8.2 mL)
PPE	=	PPE efficacy, 0.1 (90% protection)
C_{dip}	=	concentration of the insecticide in the dipping solution (from product label)
BW	=	body weight (60 kg)
AT	=	averaging time (365 days)

6.4 Accidental swallowing of concentrated formulations

When dipping is done in a domestic environment, it is possible that young children may get hold of, and accidentally swallow, a concentrated insecticide formulation (tablets, powder, or liquid). Depending on the acute toxicity of the insecticide, such situations may be life-threatening.

For the exposure scenario, if the insecticide formulation is packaged in single-net treatment size, it should be assumed that the whole of a single tablet or sachet of powder is ingested. If a multi-dose formulation is used, it should be assumed that a mouthful (20 mL or 20 g) is ingested. The amount of insecticide in the formulation will be available from the manufacturer or indicated on the package label or accompanying instructions. Signs of toxicity may be expected when the estimated dose exceeds the TSD_{AC} (see *Section 3.3*). The likelihood of serious poisoning may be estimated by comparing the estimated dose with information on the acute toxicity data of the a.i.

Intentional misuses such as disposal of dipping solutions directly into waterways may lead to adverse effects on the aqueous environment. Similarly, 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**.

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