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Ships and marine technology — Risk assessment on anti-fouling systems on ships —

Part 3: Human health risk assessment method of biocidally active substances used in anti-fouling paints on ships during the application and removal processes

Navires et technologie maritime — Évaluation des risques pour les systèmes antisalissure sur les navires —

Partie 3: Méthode d'évaluation du risque pour la santé humaine des substances bioacidement actives dans les peintures antisalissure sur les navires durant les processus d'application et d'élimination

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

The committee responsible for this document is ISO/TC 8, *Ships and marine technology*, Subcommittee SC 2, *Marine environment protection*.

ISO 13073 consists of the following parts, under the general title *Ships and marine technology — Risk assessment on anti-fouling systems on ships*:

— *Part 1: Marine environmental risk assessment method of biocidally active substances used for anti-fouling systems on ships*

— *Part 2: Marine environmental risk assessment method for anti-fouling systems on ships using biocidally active substances*

— *Part 3: Human health risk assessment method of biocidally active substances used in anti-fouling paints on ships during the application and removal processes*

Introduction

The attachment of fouling organisms, such as barnacles and algae, on the submerged parts of a ship's hull increases the propulsive resistance of the hull against water, leading to increased fuel consumption. In addition, this may also result in accidental introduction of non-indigenous species to a foreign marine environment, which may possibly cause significant and harmful impact on the local environment. In order to prevent such circumstances, an anti-fouling system that employs biocidally active substances (e.g. anti-fouling paint) to prevent attachment of fouling organisms can be applied onto the hull of the ship. The harmful effects of organotin compounds used in the maritime industry as biocides against marine organisms have been of global concern on human health. To prevent the continued use of these compounds, the International Convention on the Control of Harmful Anti-fouling Systems on Ships (the AFS Convention) was adopted at the International Maritime Organization (IMO) diplomatic conference held in London in October 2001 and entered into force in September 2008.

The Convention envisages handling various harmful anti-fouling systems within its framework and lays out a process by which anti-fouling systems can be risk assessed. Annexes 2 and 3 of the Convention include the list of information needed to determine whether an anti-fouling system is harmful to the environment and should be restricted from use on ships; however, a marine environmental risk assessment method for making this decision is not provided. There is a global need for an international assessment method for scientific environmental risk assessment for biocidally active ingredients being substituted for organotin biocides in anti-fouling systems.

ISO 13073-1 and ISO 13073-2 specify the risk assessment methods for biocidally active substances and anti-fouling systems containing the biocidally active substances, respectively. In addition to these risk assessments to protect the delicate marine ecosystems, there is also a need for protecting human health. Anti-fouling paints, which are the most commonly used anti-fouling systems to ships, potentially result in risk to the workers applying or removing them.

This part of ISO 13073 describes a method which allows a pragmatic approach to introducing human health risk assessment particularly for the workers engaged in anti-fouling paint application and removal operations. This method provides comprehensive guidelines for a risk assessment that helps protect workers in countries without a self-regulation or approval system on anti-fouling paints or those with a less well-developed system.

Ships and marine technology — Risk assessment on anti-fouling systems on ships —

Part 3:
Human health risk assessment method of biocidally active substances used in anti-fouling paints on ships during the application and removal processes

1 Scope

This part of ISO 13073 specifies a method of human health risk assessment that enables the evaluation of anti-fouling paint application and removal in order to determine if the product can be used safely where users are at risk of being exposed to biocidally active substances contained within anti-fouling paints. This can be used for a risk assessment to determine the impact(s), if any, on professional or non-professional operators.

This part of ISO 13073 does not specify a specific test method for evaluation of hazard and toxicity or recommend usage restrictions of certain substances.

NOTE 1 This part of ISO 13073 is a “minimum” method, i.e. additional regulations or assessments based on national needs can be warranted.

NOTE 2 While the approach prescribed is a tiered system, studies required in higher tiers can be undertaken in lieu of equivalent lower tier studies.

2 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

NOTE Some of the definitions for environmental risk assessment provided in ISO 13073-1 and ISO 13073-2 may be different from those of this part of ISO 13073.

2.1
adverse effect
change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of its functional capacity or impairment of its capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences

Note 1 to entry: This definition is given in reference WHO/IPCS, 1994 [63].

2.2
anti-fouling paint
type of anti-fouling system supplied as a form of paint typically consisting of a matrix polymer, pigment(s) and solvent(s)

2.3
anti-fouling system
coating, paint, surface treatment, surface, or device that is used on a ship to control or prevent attachment of unwanted organisms

Note 1 to entry: Systems of control utilizing only physical means are not included within this International Standard.

2.4
biocidally active substance
substance having general or specific action such as mortality, growth inhibition, or repellence, on unwanted fouling organisms, used in anti-fouling systems, for the prevention of attachment of sessile organisms

2.5
by-stander
person who is not a direct user of the product or application/removal equipment but who nevertheless may be exposed to the product during its use

2.6
chemical substance
chemical element or its compound in the natural state or obtained by any manufacturing process

2.7
core data
information
study
basic data, information or study which should, in principle, be provided for all biocidally active substances

2.8
expert
person with great knowledge or skill in hazard assessment of chemicals certified by academic society, organization or authority

Note 1 to entry: Those experts include Diplomat of American Board of Toxicology (USA), Fellow of the American Toxicological Society (USA), Diplomat of Japanese Society of Toxicology (Japan), European Registered Toxicologist (EU), Diploma, Korean Board of Toxicology (Korea), Expert in Toxicology, DGPT: sponsored by the German Society of Experimental and Clinical Pharmacology and Toxicology (Germany), UK Register of Toxicologists: sponsored by the Society of Biology and the British Toxicology Society (UK) and Diplomat of the Chinese Society of Toxicology (China).

2.9
exposure assessment
estimation of the range of possible doses (of a biocidally active substance, its degradants and/or metabolites) to individuals (operators) exposed to the biocidally active substance, taking into account the magnitude, frequency, duration, route, and extent (number of people) of exposure

2.10
exposure scenario
set of conditions estimating or clarifying the exposure pathways of a chemical substance to the operator

Note 1 to entry: The exposure scenario should describe the conditions of use, including, but not limited to, routes of exposure, application method, protective equipment used, job duration, etc.

2.11
hazard assessment
process to identify and characterize the adverse effects of a biocidally active substance to which individuals could be exposed

Note 1 to entry: Effects should be assessed adverse only if they affect the viability and normal function of the organism under test.

2.12
lowest observed adverse effect level
LOAEL
lowest tested dose or exposure level at which there are statistically significant increases in frequency or severity of adverse effects between the exposed population and an appropriate control group

2.13
lowest observed effect level
LOEL
lowest concentration or amount of a substance, found by experiment or observation, that causes any alteration in morphology, functional capacity, growth, development, or life span of target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure

Note 1 to entry: This definition is given in reference IUPAC Compendium of Chemical Terminology Second Edition; 1997.

2.14
margin of exposure
MOE
ratio of the no observed adverse effect level (NOAEL) to the estimated exposure dose

Note 1 to entry: MOE is also defined as the following formula:

$$\mathrm{MOE}=\frac{\mathrm{NOAEL}}{\mathrm{EXPOSURE}}$$

Note 2 to entry: MOE is used for toxic effects other than non-threshold oncogenic effects. For non-threshold oncogenic effects, then a lifetime exposure analysis with a unit risk should be developed.

Note 3 to entry: This definition is given in reference USEPA.

2.15
no observed adverse effect level
NOAEL
highest tested dose or exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control

Note 1 to entry: Some effects may be produced at this level, but they are not considered as adverse or as precursors to adverse effects.

2.16
no observed effect level
NOEL
greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure

Note 1 to entry: This definition is given in reference IUPAC Compendium of Chemical Terminology Second Edition; 1997.

2.17
non-professional operator
user of the anti-fouling paint, who is considered not to have received specific training relevant to the application or removal of anti-fouling paints and is also known as a consumer, Do It Yourself (DIY) or “amateur” user

2.18
operator
person applying and/or removing the anti-fouling paint

2.19
potential exposure rate
total amount of a defined substance found on the outer layers of clothing or overalls, plus the amount of substance found on subsequent layers inside the outer layer plus the amount of substance found on the skin

2.20
professional operator
user of the anti-fouling paint who has been formally trained in the use of both application or removal equipment and in the use of protective clothing necessary for the task

2.21
risk
combination of the probability and the severity of an adverse effect caused by exposure to a chemical substance under defined conditions

2.22
risk assessment
process intended to quantitatively or qualitatively estimate the risk posed by exposure to a substance

Note 1 to entry: A risk assessment may be qualitatively performed in case data on dose-response is insufficient to define a NOAEL (threshold dose).

2.23
risk characterization
estimation of the incidence and severity of the adverse effects likely to occur in a human population due to actual or predicted exposure to a substance

Note 1 to entry: Risk characterization may include "risk estimation", i.e. the quantification of that likelihood.

2.24
ships
vessels of any type whatsoever operating in the marine environment including hydrofoil boats, air-cushion vehicles, submersibles, floating craft, fixed or floating platforms, floating storage units (FSUs) and floating production storage and off-loading units (FPSOs)

2.25
systemic dose
amount of biocidally active substance absorbed by the exposed individual (operator)

2.26
uncertainty factor(s)
UF(s)
factor(s) used to derive a safe dose for humans with (most often) an experimental NOAEL as a starting point

Note 1 to entry: For animal data, a 100-fold uncertainty factor is usually applied to the NOAEL, which includes a 10-fold factor to allow for differences between animals and an average human, and 10-fold to allow for differences between average humans and sensitive sub-groups (WHO/IPCS, 1987 [61]). Where data exists on the level of effects shown in humans versus animals, for example, in physiologically based kinetic effects, then a lower factor may be employed on a case-by-case basis.

2.27
worst case scenario
realistic scenario in which operators are expected to be most exposed to the biocidally active substance

2.28
50 % lethal concentration
LC50
concentration at which 50 % of the test organisms would die in an experiment

3 General principles

3.1 Application

This part of ISO 13073 can be used for the risk assessment of users exposed to anti-fouling paints (i.e. painters) and other individuals exposed during the application of paint (such as co-workers or painting assistants) for the purpose of protecting persons from unacceptable exposure to biocidally active substances used in anti-fouling paints. Both professional and non-professional operators can be assessed; special attention should be paid to ensuring that the exposure scenarios which most accurately reflect the activities involved are chosen.

This part of ISO 13073 provides minimum guidelines for the following uses:

— regulation of anti-fouling paints by government organizations;

— self-regulation or approval systems carried out for industries or industrial organizations or other third parties;

— evaluations conducted for product development by industries.

Risk assessment shall be conducted for biocidally active substances including their impurities if they meet the requirements for classification as health hazards according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

This part of ISO 13073 will enable quantification of the risk posed to operators handling an anti-fouling paint containing a biocidally active substance.

3.2 Application consideration

This part of ISO 13073 shall be used with considerations described below.

— This part of ISO 13073 provides a method for evaluating the risk of a biocidally active substance (and its relevant metabolites) when applying or removing anti-fouling paints. It does not directly regulate or approve the use or commercialization of the substance.

— This part of ISO 13073 does not include a method for general risk assessment of industrial chemical substances based on the assumption that it can be carried out adequately by other methods.

— When using this part of ISO 13073 in systems of regulation, approval or use of a biocidally active substance which is demonstrated as not having an acceptable risk assessment at Tier 1 and Tier 2 shall be restricted and the substance shall be evaluated according to the process of Tier 3. These restrictions shall be established by considering the potential severity of the substance on the persons potentially exposed.

All data submitted by an applicant are considered the property of the applicant under this part of ISO 13073. These data shall not be made available to other applicants without prior written approval from the owner of the data.

3.3 Structure and procedure of human health risk assessment

Human health risk assessment consists of three procedures: exposure assessment, hazard assessment and risk characterization (see Figure 1). Exposure assessment is a procedure to estimate the dose that the persons receive, while the hazard assessment aims at defining the dose at which a potential health effect would be expected. If a threshold dose (i.e. a safe dose) cannot be found, qualitative hazard assessment should be applied.

Risk characterization is the final phase of the human health risk assessment process. It integrates hazard assessment and exposure assessment. This phase determines the probability of an adverse effect to human health at the estimated exposure levels. The quantitative risk characterization is shown

as a “margin of exposure (MOE)” using the data derived from the exposure and hazard assessments. The MOE is a quantitative index for the risk assessment.

Detailed procedures of the risk assessment are given in Annex A.

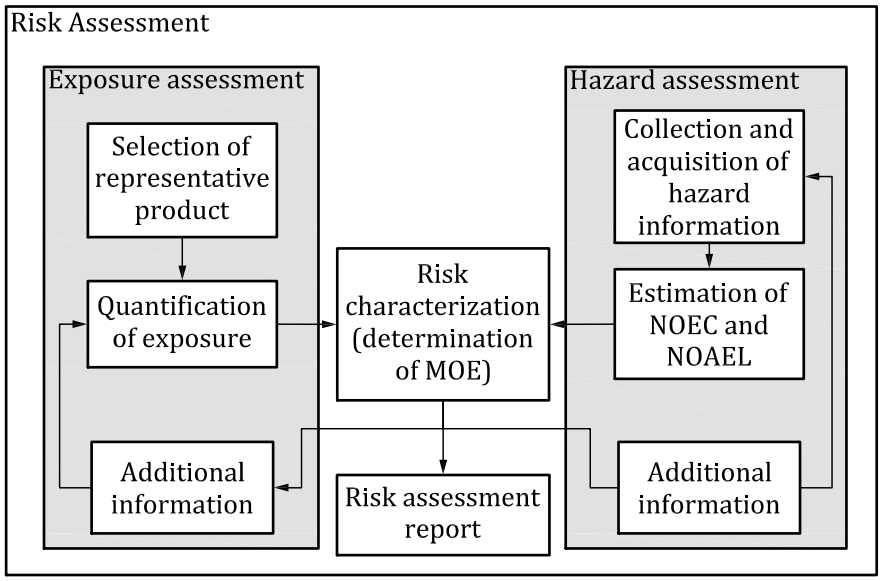


Figure 1 — Composition and schematic procedure of human health risk assessment

4 Exposure assessment

4.1 Selection of a representative product

A representative product for exposure assessment shall be selected to ensure that the anti-fouling paint contains the biocidally active substance to be assessed. In order to assume the worst case, the product chosen shall contain the highest concentration of the biocidally active substance as proposed for use in the marketplace. If no product exists in the marketplace, an experimental product can be used where the level of biocidally active substance has been found to return acceptable anti-fouling performance.

4.2 Defining the exposure scenario

4.2.1 General

An exposure scenario defines the route of exposure and potential level of exposure for the exposed individuals carrying out the activity under consideration. The scenario defined shall consider all elements of the task involved in order to model the exposure as accurately as possible for determining the dose received by the person using the product.

Examples of existing human exposure scenarios can be found in Annex B.

4.2.2 Types of exposure to consider

The risk assessment shall take into account all people who are likely to be exposed to the paint during application or removal. This will depend upon the intended use scenario and could include the use by either professional or non-professional operators [Consumers or Do It Yourself, (DIY)].

It is important to define activities of persons that will be exposed to the product during use. For example, in a dockyard, the following personnel may be exposed:

— sprayers;

— other persons in close contact with the sprayer such as boom operators;

— pot-men (operators using spray pumps to supply the sprayers);

— by-standers, etc.

Similar considerations should be given to all other use scenarios such as boatyards.

4.2.3 Determination of a representative exposure

Once the persons who will be exposed have been identified, the task should be defined, i.e. the parameters governing the amount of exposure that the person will receive. The following considerations shall be taken into account:

a) the application/removal method(s):

   1) airless spray;

   2) brush and roller;

   3) blast cleaning;

   4) all other application and removing processes (e.g. sand papering, ultra high pressure water jetting);

b) the actual exposure period for each activity of the person in a given day;

   NOTE For example, a person spraying paints may only do so for 3 h during a normal working day because time will be required for preparing equipment for use/meal breaks/waiting, etc.

c) frequency and duration of exposure (days per month or year);

d) level of personal protective equipment (PPE).

NOTE It is important to determine how much protection is offered by the equipment.

Defining the parameters mentioned above for the exposure will provide the baseline data to establish how much paint the worker is exposed to, that is how much paint comes into contact with skin (dermal exposure) or is inhaled.

NOTE Inhalation exposure should take account of the respirable fraction of any particles.

4.3 Determination of dose

Once the exposure scenario parameters have been determined, the potential dose can be calculated. In order to determine the total potential exposure to the paint, define the rate of exposure when applied using the application/removal method of interest. In simple terms, the amount of paint that is deposited on the worker's overalls and the concentration of paint in the working atmosphere shall be determined. There are two principal ways to define the potential exposure rate:

— measured data from worker's exposure studies;

— extrapolation of existing exposure data for comparable methods.

Once the potential exposure rate is known, the actual exposure to the paint shall be determined by taking into account the protection afforded to the operator by the PPE and the length of time taken to complete that task.

To determine the actual dose from the exposure to the paint, the following data are needed:

— the content of the biocidally active substance in the paint which is typically expressed in % weight/weight wet paint (%w/w wet paint) terms;

— the absorption of the biocidally active substance from the paint across the skin;

— the absorption of the biocidally active substance from the paint across the lungs.

The concentration of the biocidally active substance in the paint can be obtained from the label on the paint can, the safety data sheet (SDS) or from the paint manufacturer.

Absorption of biocidally active substances through the skin should preferably be determined from a dermal absorption study with a representative paint containing the biocidally active substance at an appropriate concentration. A combination of the results of the OECD guidelines 427 (*in vivo*, rats) and 428 (*in vitro*) provide good methods for dermal absorption evaluation. *In vitro* studies with human skin according to OECD guidelines 428 as stand-alone test are also accepted. Where no test data is available, an appropriate default value may be selected.

For exposure by inhalation, it shall be determined whether the adverse effect is local or systemic.

For local effects (irritation/corrosion, sensitization), inhalation and dermal exposure shall be assessed separately. For systemic effects, inhalation and dermal exposure shall be assessed together when the critical endpoint is common but may be assessed separately where the critical endpoints are different.

By using the exposure data and the dermal/lung absorption data, the amount of biocidally active substance which passes across relevant biological membranes can be determined and the systemic dose calculated by taking into account the typical weight of the operator exposed. Generally, this is expressed in terms of exposure per unit body weight (bw) of operator per day (i.e. mg biocidally active substance/kg bw/day).

An example of existing human exposure scenarios for preparing emission scenarios can be found in the Technical Notes for Guidance (TNsG) for Human Risk Assessment developed for the Biocidal Products Directive (98/8/EC). Further details regarding determining exposure are given in Annex C.

5 Hazard assessment

5.1 Data and information

5.1.1 Collection and acquisition of data and information

In order to conduct the assessment appropriately, studies to identify the physico-chemical or hazardous properties of the biocidally active substance (and, where necessary, its metabolites) should be conducted in accordance with International Standards. Examples of studies are provided in Annex E.

Data and information to identify the physico-chemical or hazardous properties of the biocidally active substance (and, where necessary, its metabolites) should be collected. Studies and data in accordance with internationally recognized test methods should be collected with priority in order to conduct the assessment appropriately.

5.1.2 Information acquisition through testing

5.1.2.1 Test implementation

Tests shall be conducted according to internationally recognized test methods, or test methods equivalent to such methods, by an organization or a laboratory meeting the Good Laboratory Practice (GLP) requirements or with the equivalent qualification. Examples of testing methods are provided in Annex E.

Due consideration should be given to minimizing the use of animals and, where appropriate, validated *in vitro* studies should be used in preference to *in vivo* studies.

5.1.2.2 Selection of test species

Unless otherwise stated in a particular test method, animals used for toxicity testing should be chosen on the basis of their suitability for the test and that their physiological response is considered analogous to that of humans or that the physiology of the organism is sufficiently well understood to allow extrapolation to human responses.

5.1.2.3 Test omission (data waiving)

Where a substantiated scientific basis has been developed, some necessary tests may be omitted and/or replaced with other test results or test methods. In each case, existing test results on structurally similar substances or other reasoning such as lack of foreseen exposure may be applicable. For example, a quantitative structural analysis-relationship (QSAR) approach may be possible. An overview of QSAR analysis can be found in the European Union Technical Guidance Document on Risk Assessment, Part III.

Mode of action studies on the substance may be particularly helpful for waiving *in vivo* studies.

5.1.3 Reliability assessment of the collected data

All studies and data used in the risk assessment shall be assessed for their quality. Unreliable data should not be used in the risk assessment process. Examples of guidance on data quality evaluation methods are shown in Annex F.

All data to be submitted as part of the risk assessment shall be evaluated for quality according to the reliability assessment. The applicant may submit data evaluated as “not reliable” or “of very low reliability”. These data may be used in a “weight of evidence” approach.

Irrespective of reliability of the data, potentially severe health effects shall be reported and accounted for.

5.1.4 Consideration of animal welfare

When planning the test program, consideration should be given to animal welfare, i.e. using the minimum number of test animals necessary. Tests should only be conducted when it is clear that the risk assessment will be improved by the tests. For example, irritation tests may be omitted regardless of the requirement in A.2.1.1 when a sequential testing strategy for irritation or corrosion studies in OECD 404 and 405 can be applied.

5.2 Defining the NOAEL

Once a hazard assessment has been conducted and the critical endpoint(s) is identified, the risk assessor shall identify the highest dose at which no critical adverse effect(s) was demonstrated. The dose (expressed as NOAEL) shall be selected from the studies judged to be most relevant to the exposure scenario being evaluated.

In order to define the no observed adverse effect level (NOAEL), the available toxicological data for the active substance shall be reviewed and considered for use according to the process given in Annex A.

6 Risk characterization

6.1 General

Risk characterization is conducted with the tiered process described in Annex A. Note that the NOAEL is calculated using toxicity data required in each tier of the process and the risk level is determined by comparing the ratio of the exposure level to the NOAEL for the most relevant exposure model (NOAEL/exposure level ratio). This ratio [margin of exposure (MOE)] is used to determine whether the risk can be considered acceptable or not.

6.2 Tiered system

The risk characterization process starts at Tier 1 and proceeds stepwise to end in Tier 3. By using a tiered approach, limited approvals can be granted at each tier enabling companies to develop further data to improve and refine the risk assessment. The tiered approach, therefore, enables placement of a product on the market with a basic data set in order that product development can continue and revenue be generated to justify further investment in studies to refine the risk assessment. Once the data criteria in Tier 3 are met, the risk assessment of the biocidally active substance can be regarded as complete.

If a biocidally active substance does not meet the criteria described in Tier 1, it implies that the substance may have an adverse effect on the exposed person. The biocidally active substance shall therefore not be considered acceptable for use unless more data is supplied to comply with the higher Tiers (Tiers 2 and 3).

Where data for a particular toxicological effect are required at multiple tiers, longer term studies may be used in lieu of short-term studies. For example, a 90-day oral exposure study can be used in place of a 28-day oral exposure study.

6.3 Consideration of uncertainty factor

The process of choosing an uncertainty factor (UF), which may sometimes be referred to as assessment factor (AF), shall account for each of the applicable areas of uncertainty. The primary reason for using UFs is to account for scientific uncertainty in the results from toxicity studies and their relevance to humans. A typical UF in common use is 100 which accounts for a 10-fold factor when extrapolating results from long-term animal studies to humans and a 10-fold factor to account for variation in sensitivity among humans. As variation in sensitivity among professionals is lower than for the general population, a lower uncertainty factor could be justified. Additional factors may be applied when deriving the reference dose (Rfd) from the lowest observed adverse effect level (LOAEL) instead of the NOAEL or utilizing subchronic data in place of chronic data, etc.

Some examples of setting the UF are described in Annex D; a combination of these methods/perspectives may be appropriate.

6.4 Characterization of risk

Following the process described in Annex A, the risk associated with a biocidally active substance used in an anti-fouling paint is determined based on the results of the test data obtained at each tier.

7 Assessment results

7.1 Decision at each tier

7.1.1 Tier 1 decision: Preliminary acceptability

Successful evaluation results in “Preliminary acceptability” at Tier 1 which is granted on the basis that data according to Tier 2 requirements will be provided in order to allow a more robust assessment to be made. A suitable time should be defined after which the data should be submitted.

Supply to the market at this stage is also restricted to professional use only.

7.1.2 Tier 2 decision: Continuing acceptability

Successful evaluation results in “Continuing acceptability” at Tier 2 which is granted on the basis that data according to Tier 3 requirements will be provided in order to allow a more robust assessment to be made. A suitable time should be defined after which the data should be submitted.

For professional use, continued supply to the market at this Tier will only be granted for products with an acceptable MOE.

Non-professional use can be allowed as long as an acceptable MOE can be demonstrated.

7.1.3 Tier 3 decision: Full acceptability

Successful evaluation results in "Full acceptability" at Tier 3. Full acceptability is allowed only for those use scenarios that have been fully evaluated. For example, biocidally active substances which have only been risk assessed for professional use shall not be made available for use by non-professional users.

It is advisable that a time limit should be placed on the acceptability after which the biocidally active substance should be re-reviewed taking into account advances in risk assessment and applying best practice. Typical acceptability periods are generally within 10 years from the date of the original evaluation.

7.2 Expert judgement

When uncertainties exist, or toxicity data in one or more areas are inadequate, the uncertainty factor (UF) should be increased. It should also be recognized that expert judgement is often necessary to define a particular endpoint. It should be ensured that data are evaluated by a competent person.

7.3 Additional information obtained after last risk assessment

Whenever additional information regarding a substance's toxicological properties becomes known, the risk assessment should be refined. This may change the earlier decision and thus the earlier conditions on use.

8 Risk assessment report

Regarding the risk assessment conducted according to this part of ISO 13073, a risk assessment report shall be prepared. The minimum required information to be cited in the risk assessment report is described in Annex G.

Annex A
(normative)

Risk characterization process for human health risk assessment of biocidally active substances used in anti-fouling paints on ships

A.1 General

This Annex specifies the decision-making process of human health risk assessment for a biocidally active substance used in anti-fouling paints on ships. This process aims at providing an appropriate risk assessment method for protecting professional and non-professional operators' health.

A.2 Step-by-step approach

The following risk assessment process shall be followed to undertake the risk assessment. The assessment is conducted in order of Tier 1, Tier 2 and then Tier 3, based on the criteria described in each step, until finally a decision is made as to whether the biocidally active substance is considered acceptable for use or not.

A.2.1 Tier 1

A.2.1.1 Data and information requirement

The core data and information required in Tier 1 are as follows:

— acute toxicity data the "6 pack" including the following:
  — acute oral toxicity;
  — acute dermal toxicity;
  — acute inhalation toxicity;
  — acute dermal irritation;
  — acute eye irritation;
  — acute dermal sensitization;
— Ames test (*Salmonella typhimurium* and *Escherichia coli*);
— physico-chemical properties:
  — molecular weight;
  — melting point, boiling point and relative density;
  — vapour pressure, flash-point and surface tension, if applicable;
  — physical state and colour;
  — water solubility (effect of pH and temperature);
  — thermal stability and decomposition product(s);
  — *n*-octanol/water partition coefficient (effect of pH and temperature).

Additional studies which may be required in Tier 1 are as follows:

— *in vitro* genotoxicity data including the following:

  — chromosome aberration – mammalian cell;

  — gene mutation – mammalian cell;

— 28-day oral toxicity study in rat with extensive pathology.

A.2.1.2 Criteria

In Tier 1, the biocidally active substance shall meet all of the criteria given in Table A.1 to qualify for preliminary acceptability. Where an acceptable margin of exposure (MOE) is not achieved, the assessment can be refined by determining a more accurate dermal absorption value for the biocidally active substance in a suitable solvent or in an appropriate paint formulation.

Table A.1 — Details of studies intended for use in Tier 1

Study	Interpretation
Acute toxicity (6 pack)	These data should be used to classify the biocidally active substance in order to define the level of protection (PPE or engineering controls) required by professional user. There are no pass or fail criteria for these studies.
In vitro genotoxicity	Ames negative or if Ames is positive, additional genotoxicity studies negative (i.e. show no genotoxicity). Chromosome aberration and gene mutation studies may be conducted using a quantitative structure activity relationship (QSAR) approach where a reliable QSAR analysis is available.
28-day oral toxicity study (if performed)	If, based on expert judgement, there is significant cause for concern due to nature of the biocidally active substance then a 28-day oral toxicity study in rat with extensive pathology shall be conducted.
Risk assessment	Preliminary MOE found to be 100 or higher (depending on shortcomings in the data source; expert judgement may be needed).
CMR assessment	No adverse effects anticipated based on existing data.
NOTE 1 Suitable models and advice on QSAR analysis include the following. Other appropriate models may be available. — OECD QSAR application tools box. Version 3.3.5. Released July 2015. Available at: http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm — Estimation Program Interface (EPI) Suite. USA EPA available at www.epa.gov — European Union Technical Guidance Document for Risk Assessment, Chapter 4. Available at https://echa.europa.eu/documents/10162/16960216/tgdpart3_2ed_en.pdf NOTE 2 In preliminary review, possibility of CMR is studied based on publicly available information and/or QSAR analysis.	

A.2.1.3 Assessment

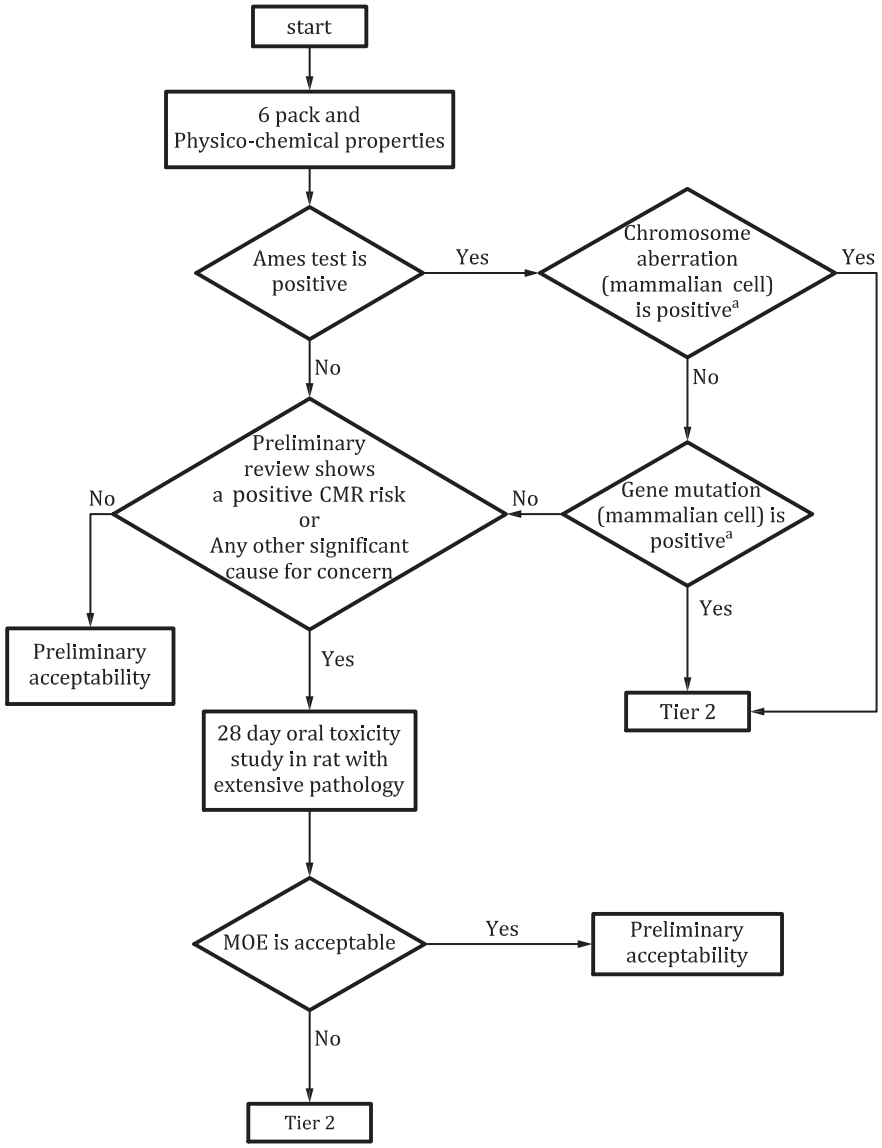
If the biocidally active substance meets the criteria in A.2.1.2, it can be granted preliminary acceptability allowing sale on the basis that

— the data requirements for Tier 1 assessment are met, and

— the acceptability carries a time limit on sales.

The evaluation flow of Tier 1 is illustrated in Figure A.1. The use shall be limited to professional operators even if the biocidally active substance passes the criteria of this Tier.

If the biocidally active substance fails any of the criteria at Tier 1, preliminary acceptability shall not be granted and the biocidally active substance shall be prevented from sale. For the biocidally active substance to be allowed for sale, assessment under the Tier 2 should be sought with the required data and information.



Key

a If QSAR is available, an assessor can use QSAR approach.

Figure A.1 — Process of risk characterization for biocidally active substances in Tier 1

A.2.2 Tier 2

The evaluation flow of Tier 2 is illustrated in Figure A.2. The data requirements for Tier 2 vary from substance to substance depending upon the results obtained in Tier 1. The selection requirements for the possible data are defined in subsequent sections below.

A.2.2.1 Core and additional data and information

The core data and information required in Tier 2 are as follows:

— metabolism study in rat; absorption, distribution, metabolism and excretion (ADME study);

— 28-day oral toxicity study in rat (if not undertaken in Tier 1);

— *in vitro* genotoxicity, including chromosome aberration – mammalian cell (if not undertaken in Tier 1);

— study on dermal absorption of the biocidally active substance in the anti-fouling paint to be assessed. Waiving may be acceptable provided that 100 % or 10 % dermal absorption depending on molecular weight and solubility of the biocidally active substance is used;

— reproductive toxicity screening study (fertility and development).

Additional data and information which may be required in Tier 2 are given below:

— *in vivo* genotoxicity, e.g.

  — mouse micronucleus,

  — unscheduled DNA synthesis,

  — mouse spot test,

  — dominant lethal mutation, and

  — others as appropriate;

— 28-day inhalation toxicity study in rat;

— 28-day dermal toxicity study in rat.

A.2.2.2 Criteria

Two criteria need to be considered at Tier 2: those necessary to decide whether the additional studies are required (see Table A.2) and those required in order to pass the risk assessment at Tier 2 (see Table A.3) and be allowed sale with a time limit.

Table A.2 — Details of studies intended for use in Tier 2

Core studies	
Study	Interpretation
Metabolism study in rat; ADME study	The data from these studies enable the interpretation of the toxicological studies noted below and inform on toxicokinetics and toxico-dynamics.
28-day oral toxicity study	Core study used to define the NOAEL.
Reprotoxicity screen	Core study used to define the NOAEL.
Additional studies	
Study	Interpretation
In vivo genotoxicity 1	Mouse micronucleus and/or unscheduled DNA tests: If one or more of Tier 1 genotoxicity studies are positive (i.e. genotoxicity is observed), an *in vivo* study is necessary at Tier 2.
In vivo genotoxicity 2	Mouse spot test/dominant lethal mutation/others as appropriate: If the results from genotoxicity study in "*in vivo* genotoxicity 1" are negative (i.e. there is no effect) then no further studies are needed. If they are positive (i.e. there is an effect), a further study shall be required which could be the "mouse spot test", "dominant lethal mutation", or others appropriate to investigating the observed effect in the first study.
28-day inhalation toxicity study in rat	This study may be necessary if the median mass aerodynamic diameter (MMAD) is below 50 µm and if the acute LC50 is below 1,0 mg/m^3.
28-day dermal toxicity study in rat	This study may be required if there is concern regarding dermal toxicity.
Dermal absorption	The absorption value obtained should be used to calculate the systemic exposure by the dermal route.

Table A.3 — Decision of Tier 2 studies

Core studies	
Study	Criteria
28-day oral toxicity study	To achieve "preliminary acceptability", adverse CMR effects or any other serious health concern shall not be observed.
Reprotoxicity screen	To "preliminary acceptability", no adverse observations shall be noted.
Additional studies (when conducted)	
Study	Criteria
Mouse micronucleus Unscheduled DNA synthesis Mouse spot test Dominant lethal mutation Others as appropriate	Expert opinion shall conclude that these preliminary data indicate that the biocidally active substance does not have a genotoxic potential and is unlikely to be carcinogenic via a genotoxic mechanism.
28-day inhalation toxicity study in rat 28-day dermal toxicity study in rat	These data should be used to define the NOAELs to be used in the human health risk assessment.
Risk assessment	Acceptable margin of exposure found (e.g. MOE ≥ 100).

A.2.2.3 Assessment

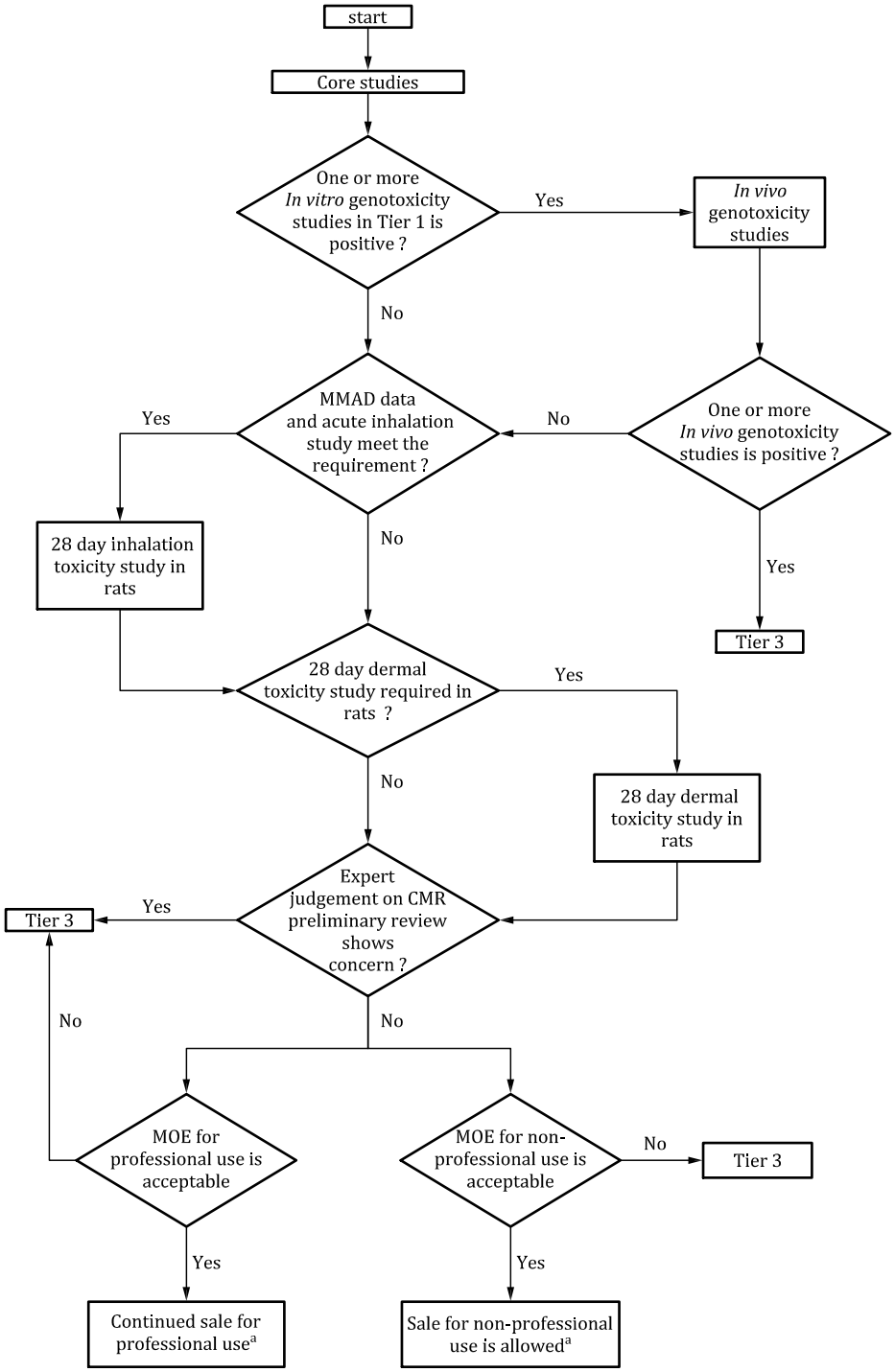
If the substance meets the criteria for the required studies for A.2.2.2, it can be granted sale on the basis that

— the data requirements for Tier 2 assessment are met, and

— the acceptability carries a time limit on sales.

Where any of the studies do not meet the acceptability criteria in A.2.2.2, an assessment under Tier 3 shall be undertaken.

Sale to professionals and non-professionals for a limited period of time would be granted if the biocidally active substance passes all the criteria at Tier 2 and the respective MOEs are acceptable. In all cases, sale shall only be granted where the biocidally active substance exhibits negative results for genotoxicity and reproductive toxicity and there are no observations of potentially serious health effects. For the biocidally active substance to be fully evaluated, assessment under Tier 3 shall be sought (with the intention of closing important data gaps).



Key

a The acceptance carries a time limit on sales.

Figure A.2 — Process of risk characterization for biocidally active substances in Tier 2

A.2.3 Tier 3

As with Tier 2, the data required to pass through this Tier will vary from substance to substance depending upon the results obtained in previous Tiers. This is handled in Figure A.3 by listing two separate data sets: core data requirements and additional requirements. However, unlike Tier 2, there are selection requirements for the core and additional data as some of the decision steps may

be satisfied by using expert judgement of the data generated in the lower Tiers. Guidance on selection criteria are defined in subsequent sections below.

A.2.3.1 Core studies and additional data and information

The core studies required in Tier 3 are as follows:

— chronic/carcinogenicity study in rat and mouse;

— multi-generation reproduction toxicity study.

Additional data and information which may be required in Tier 3 are as follows:

— teratogenicity study;

— subchronic or chronic inhalation study in rat;

— subchronic or chronic dermal study in rat;

— developmental neurotoxicity;

— immunotoxicity;

— mode of action.

A.2.3.2 Criteria

Two criteria need to be considered at Tier 3: those necessary to decide whether the additional studies are required (see Table A.4) and those required in order to pass the risk assessment at Tier 3 (see Table A.5) and be allowed continued sale.

Table A.4 — Details of studies intended for use in Tier 3

Core studies	
Study	Interpretation
Chronic/carcinogenicity study in rat Chronic/carcinogenicity study in mouse	Core studies unless non-submission waivers can be established based upon expert judgement using available data from Tiers 1 and 2.
Multi-generation reproduction toxicity study	Core studies unless it is scientifically justified that it can be excluded (e.g. based on screening study under Tier 2).
Additional studies	
Study	Interpretation
Teratogenicity study	This study should be required if concern arises from the multi-generation studies.
Subchronic or chronic inhalation study in rat	This study may not be necessary if the MMAD of the substance is greater than 50 µm and it is scientifically justified that it can be excluded.
Subchronic or chronic dermal study in rat	This study should not be required unless it is scientifically justified that this administration route would represent serious concern.
Developmental neurotoxicity	This study may only be necessary if expert review of repeat dose studies suggests a possible neurotoxicological endpoint, e.g. histopathological findings in the central nervous system.
Immunotoxicity study	This study may only be necessary if expert review of repeat dose studies suggests a possible immunotoxicological endpoint, e.g. reduced thymus weight/atrophy.
Mode of action	Studies may be chosen on a case by case basis to address critical endpoints and relevance to human health.

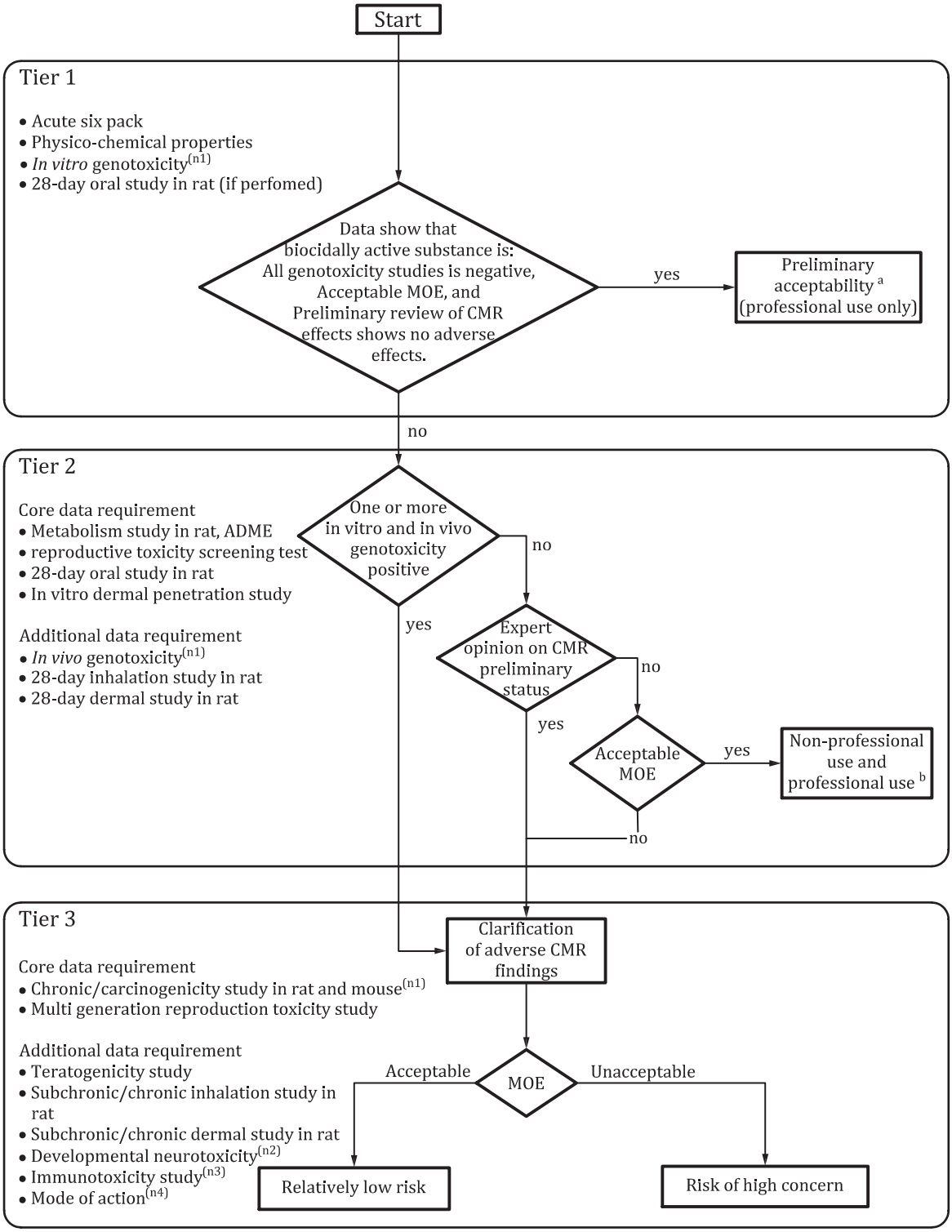
Table A.5 — Decision of Tier 3 studies

Core studies	
Study	Criteria
Chronic/carcinogenicity study in rat Chronic/carcinogenicity study in mouse	Biocidally active substance not considered to be a non-threshold carcinogen. If it is non-mutagenic, NOAEL should be used.
Multi-generation reproduction toxicity study	This study should be used to define the NOAEL to be used in the human health risk assessment.
Additional studies	
Study	Criteria
Teratogenicity study	This study should be used to define the NOAEL to be used in the human health risk assessment.
Subchronic or chronic inhalation study in rat	This study should be used to define the NOAEL to be used in the human health risk assessment.
Subchronic or chronic dermal study in rat	This study should be used to define the NOAEL to be used in the human health risk assessment.
Developmental neurotoxicity	This study should be used to define the NOAEL to be used in the human health risk assessment.
Immunotoxicity study	This study should be used to define the NOAEL to be used in the human health risk assessment.
Mode of action	If concerns still remain about effects on humans, other studies to elucidate the mode of action can be considered. For example, a physiologically based pharmacokinetic (PBPK) model demonstrating its relevance to humans would be appropriate for consideration of continued sales.
Risk assessment	Acceptable margin of exposure (e.g. MOE ≥ 100).

A.2.3.3 Assessment

If the substance meets the criteria for the studies for A.2.3.2, it can be granted for sale on the basis that risk has been found acceptable for the applicable exposure scenarios.

It is recommended that a time limit is set for re-evaluation of the biocidally active substance. A 10-year time limit is typical in existing regulatory programmes.



Key

a Risk assessment (RA) acceptable margin of exposure (MOE) is conducted assuming either 100 % of 10 % dermal absorption depending on molecular weight and solubility of the biocidally active substance. Dermal absorption data can be used to refine the values if necessary.

"Preliminary acceptability" at Tier 1 means that sale should only be allowed on the basis that the Tier 2 data will be provided to enable a more robust assessment. A suitable time limit should be set after which the data should be provided.

b "Non-professional use and professional use" at Tier 2 mean that sale should be allowed on the basis that Tier 3 data will be provided to enable a more robust assessment. A suitable time limit should be set after which the data should be provided.

c Even if the biocidally active substance is still deemed as CMR, use may be allowed as long as it has threshold value and MOE is acceptable.

Tier 2

n1 If one or more of the Tier 1 genotoxicity assays are positive, then it is a core data requirement to conduct an *in vivo* study at Tier 2 (e.g. mouse micronucleus, unscheduled DNA synthesis). If that assay is negative, there is no need to do any further genotoxicity assays. If that assay is positive, then a further *in vivo* study is indicated, which can be mouse spot test, dominant lethal mutation or others as appropriate. In the event that all three of the Tier 1 genotoxicity studies are negative, the Tier 2 *in vivo* studies can be used as the basis for waiving carcinogenicity studies.

Tier 3

n1 Core study unless waiver is established based on expert judgement using available data from Tiers 1 and 2.

n2 This study may only be necessary if there is significant concern about chemicals with similar structure or expert review of repeat dose studies suggests a possible neurotoxicological endpoint (e.g. histopathological findings in the central nervous system).

n3 This study may only be necessary if there is any significant concern about chemicals with similar structure or if expert review of repeated dose studies suggests a possible immunological response (e.g. reduced thymus weight/atrophy).

n4 Studies should be chosen on a case-by-case basis to address the critical endpoint(s).

Figure A.3 — Process of risk characterization for biocidally active substances

Annex B
(informative)

Examples of operator exposure models

B.1 General

This Annex describes existing model samples for estimating exposure to operators involved in application/removal work of anti-fouling paints. It is recommended that the latest revisions of the exposure models should be consulted as they may be continuously amended.

B.2 Technical Notes for Guidance (TNsG) for risk assessment conforming to the EU Biocidal Products Directive (BPD)

A collection of exposure data is provided either in a database or described in summary format in TNsG (2007), Annex 1. In the TNsG, available generic data models are shown (see TNsG, Section 5 and Annex 1). This is intended to simplify the process of identifying suitable data and allows for more regular updating of the guidance. The latest information is available in ECHA (2013) Guidance for Human Health Risk Assessment, Chapter 3.

Sample format for exposure assessments is shown in Annex C.

B.3 Other models

B.3.1 EUSES

European Union System for the Evaluation of Substances (EUSES) is designed to be a decision-support system which enables government authorities, research institutes and chemical companies to carry out rapid and efficient assessments of the general risks posed by chemical substances. EUSES is intended mainly for initial and refined risk assessments rather than for comprehensive assessments. The system is fully described in the EUSES documentation and is based on the EU Technical Guidance Documents (TGDs, EC-TGD, 2003) for risk assessment of new and existing substances and biocides.

B.3.2 EASE

Estimation and Assessment of Substance Exposure (EASE) is a general model described in TGD, 2.2. EASE was specifically developed by the Health and Safety Executive (HSE), UK, for the purpose of modelling inhalation and dermal workplace exposure across a wide range of circumstances. EASE is an analogue model, i.e. it is based on measured data that are assigned to specific scenarios.

B.3.3 ChemSTEER

ChemSTEER estimates occupational inhalation and dermal exposure to a chemical during industrial and commercial manufacturing, processing, and use operations involving the chemical.

ChemSTEER estimates releases of a chemical to air, water and land that are associated with industrial and commercial manufacturing, processing and use of the chemical.

ChemSTEER can be downloaded from http://www2.epa.gov/tsca-screening-tools/chemsteer-chemical-screening-tool-exposures-and-environmental-releases.

B.3.4 BEAT

The Bayesian Exposure Assessment Toolkit (BEAT) has been developed, by the Health and Safety Executive (HSE), UK, for assessing dermal and inhalation exposure in a wide variety of scenarios, specifically for assessment of biocidal products. BEAT provides users flexibility for selection of specific data sets or mixed data sets providing an amended exposure estimate for similar but different scenarios. The users need to obtain expert judgement when selecting the data sets.

The computerized version of BEAT is available from http://xnet.hsl.gov.uk/download/.

B.3.5 ConsExpo

ConsExpo is a computer program that has been developed to assist the exposure assessment of the compounds in non-food consumer products. A wide range of available consumer products are associated with an even wider variation in consumers and in product uses. Measured data on exposure to compounds in products is not always available. Even in the absence of these data, ConsExpo can be used to estimate the exposure for different exposure scenarios. The program offers a number of generally applicable exposure models and a database of exposure factors for a broad set of consumer products. Together, the models and the database provide a tool to estimate an exposure for a wide range of consumer products, whereby only basic information on the product composition and the physicochemical properties of the compound of interest are needed.

ConsExpo can be downloaded from http://www.rivm.nl/en/Topics/C/ConsExpo.

Annex C
(informative)

Predicting operator exposure values

C.1 Biocidal products directive (98/8/EC)

Since it is easy to make arithmetical errors in simple deterministic calculations, the following simple routine is provided as an example of a typical spreadsheet based calculation sheet to determine human exposure to anti-fouling paints (see Table C.1). This can be copied and pasted directly into a suitable spreadsheet programme if required.

Table C.1 — Examples of typical predicted operator exposure values for the Biocidal Products Directives

CELL A	B	C	D	E
1	**General exposure calculator**		**[title]**	
2	Product		Calculation	Units
3	active substance		D3	%
4	density		D4	g/ml (if w/v)
5				
6	**Potential dermal exposure**		value	
7	indicative value	from model	D7	mg/min
8	duration		D8	min
9	potential dermal deposit		D7 × D8	mg
10	clothing penetration	from model	D10	%
11	actual dermal deposit (product)		D9 × D10/100	mg
12				
13	**Hand in gloves exposure**		value	
14	indicative value	from model	D14	mg/min
15	duration		D8	min
16	actual hand deposit (product)		D14 × D8	mg
17				
18	**Foot in shoe exposure**		value	
19	indicative value	from model	D19	mg/min
20	duration		D8	min
21	actual foot deposit (product)		D19 × D8	mg
22				
23	**Actual dermal exposure**			
24	product		D11 + D16 + D21	mg
25	active substance		D24 × D3/100	mg
26				
27	skin penetration		D27	%
28	active substance via the skin		D25 × D27/100	mg
29				

Table C.1 *(continued)*

CELL A	B	C	D	E
30	Exposure by inhalation		value	
31	indicative value	from model	D31	mg/m^3
32	duration		D8	min
33	inhalation rate		D33	m^3/min
34	inhaled volume		D33 × D8	m^3
35	inhaled (product)		D31 × D34	mg
36	active substance		D35 × D3/100	mg
37				
38	Dose			
39	total		D28 + D36	mg
40	body-weight		D40	kg
41	systemic dose		D39/D40	mg/kg bw

This calculator assumes all products have a density of 1,0. Errors in correcting for density are unlikely to exceed the errors in sampling. However, this single-event calculator produces erroneous results when multiple events are modelled. When the input values are taken from data distributions, the magnitude of the error depends on the percentile and the number of events. Such considerations should be taken into account when calculating exposure to anti-fouling paints as paint densities can vary significantly from 1,0.

C.2 Information needs for workplace exposure assessment

In order to provide assessors with sufficient data to reliably and accurately estimate exposure via the different routes, there is a need for information both which describes the nature and degree of exposure and which, ideally, is supported by quantified data. In view of the uncertainties associated with assessing exposure in human populations, preference should always be given to obtaining representative measured exposure data. Where this is unavailable, analogous/surrogate data should be used.

Measured exposure data and associated information describing these data may be available from workplace exposure assessments and routine monitoring regimes. Such information may also be available from dedicated surveys or from work with analogous substances having close chemical and physical properties. Current information may be available from the relevant literature and should also be seen as a source of information. All data require careful evaluation before use. Data should be accompanied by sufficient information to place the exposures in context with respect to the pattern of use, pattern of control and other relevant process parameters. Data may also be available that describe the frequency and duration of exposure with respect to these parameters. The data should have been collected following good occupational hygiene practice, preferably employing standardized procedures, particularly with respect to sampling strategy and measurement methods. Where possible, documents such as those from the European Committee for Standardization (CEN) or other relevant International Standards should be used as the basis both for the sampling strategy and associated measurement and for analytical techniques (e.g. ENs 689, 481 and 482).

In some circumstances, analogous/surrogate measured data may be used instead of, or as well as, measurement data for the substance under assessment, e.g. when there are few measurement data for the specific substance. For the purposes of exposure assessment, analogous/surrogate data describe data from similar operations utilizing the same substance or data for the same operation but for similar substances. It is considered that most substances will have analogous/surrogate markers which, while not providing equivalent reliability in terms of their status in the data hierarchy, provide information which is more valuable than that obtained from modelled estimates.

C.3 Other useful information for workplace exposure assessment

The following information is useful for workplace exposure assessment.

— Manual of Technical Agreements (MOTA) Biocides Technical Meeting, Version 6; 2013, https://echa.europa.eu/documents/10162/19680902/mota_v6_en.doc

— Antifouling painting model – Amendment of TNsG on Human exposure to biocidal products HEEG Opinion agreed at TM II 08

Annex D
(informative)

Examples of setting of uncertainty factor (UF)

D.1 General

This part of ISO 13073 requires assessment of hazardous effects taking into account variability and uncertainty within and between species. All these uncertainties/differences are individually addressed by so-called uncertainty factors (UFs), that together result in an overall UF that is applied to the corrected dose descriptor.

Preferably, the value for each individual uncertainty factor is based on substance-specific information. However, although sound in principle, in practice, the approach has limitations (data are often scarce, especially toxico-dynamic data and human data) so that several extrapolation steps may be needed if such heterogeneous data are to be used to characterize the risk for humans.

Therefore, default uncertainty factors most often need to be used. Each step in the process, including any choice for an uncertainty factor value, whether substance-specific or default should be explained as transparently as possible, with a qualitative narrative in the risk assessment report.

D.2 Setting individual UFs

D.2.1 Aspects to be considered in setting UFs

Several aspects are involved in the extrapolation of experimental data to the human situation. The following aspects need to be taken into account:

— inter-species differences (differences in toxicokinetics and toxico-dynamics);

— intra-species differences (differences in susceptibility);

— differences in duration/frequency of exposure (with relevance to human exposure);

— differences between routes of exposure;

— issues related to dose-response (e.g. threshold or not, nature and severity of effect, etc.);

— quality of the study (strength of evidence);

— quality of whole data set (weight of evidence).

Defaults typically proposed for human health risk assessment are point estimates. A more recent development is the suggestion for probabilistic distributions as defaults for uncertainty factors, as lognormal distributions are thought to best describe variability and uncertainty in uncertainty factors; these distributions have been derived based on NOAEL-ratios from comprehensive toxicological databases. Although promising, up to now, these probabilistic distributions have not been widely used in risk uncertainty and others because it requires decisions on the percentile of the population one wants to protect [e.g. 50th percentile (= geometric mean of distribution) or 90th, 95th or 99th percentile (= P90, P95 or P99 of distribution)].

D.2.2 Uncertainty factors for inter-species differences

Inter-species differences result from variation in the sensitivity of species due to differences in toxicokinetics and toxico-dynamics. Where human data are used as the starting point for the risk

characterization, no extrapolation is normally necessary and hence no uncertainty factor is suggested for interspecies differences in sensitivity.

Where data from animal studies are the typical starting point for risk characterization, the default assumption in general is that humans are more sensitive than experimental animals. As can be seen from Table D.1, the traditional default suggested for interspecies extrapolation is 10, which sometimes is subdivided in a default of 4 for toxicokinetic differences and a default of 2,5 for toxico-dynamic differences.

Since some of the toxicokinetic differences can be explained by differences in body size (and related differences in basal metabolic rate), others have suggested as a default to, where appropriate, correct for differences in metabolic rate (allometric scaling), followed by the application of a default factor for other toxicokinetic and toxico-dynamic differences. Next to these point estimates, also default lognormal distributions have been established for this additional factor.

D.2.3 Uncertainty factors for intra-species differences

Humans differ in sensitivity due to a number of biological factors (such as age, gender, genetic composition and nutritional status). The intra-species variation in humans is greater than in the more homogeneous experimental animal population.

Although other values have been proposed, defaults typically suggested for the general population (representing all age groups, including children and elderly) are a factor of 10, sometimes equally subdivided in defaults of 3,16 for both toxicokinetic and toxico-dynamic differences. A lower default factor is generally suggested for the worker population because the very young and very old are not part of this population.

For the intra-species uncertainty factor, also probabilistic distributions have been proposed. It is to be noted that the ones proposed by Vermeire et al.[59][60] are not database-derived distributions but theoretical distributions.

D.2.4 Uncertainty factors for differences in duration/frequency of exposure

In general, the experimental NOAEL will decrease with increasing exposure duration. In extrapolation, from e.g. a short-term NOAEL to a long-term NOAEL, a factor is applied.

As can be seen in Table D.1, different factors have been suggested for exposure duration extrapolation, depending on the type of extrapolation (subacute to subchronic, subchronic to chronic, subacute to chronic) and the kind of effect (systemic or local). Probabilistic distributions have also been suggested.

D.2.5 Route-to-route extrapolation

When extrapolating from one route of administration to another (e.g. from oral to inhalation), normally, 100 % systemic absorption is set as default unless valid data is available.

D.2.6 Uncertainty factor for dose-response relationship

For the dose-response relationship, consideration should be given to the uncertainties in the NOAEL as the surrogate for the true no adverse effect level (NAEL), as well as to the extrapolation of the LOAEL to the NAEL (in cases where only a LOAEL is available or where a LOAEL is considered a more appropriate starting point). Taking into account the dose spacing in the experiment, the shape and slope of the dose-response curve (and in some approaches, the extent and severity of the effect seen at the LOAEL), defaults typically suggested for this uncertainty factor range from 1 to 10 (see Table D.1). The benchmark dose has also been suggested as acceptable alternative to the LOAEL-NAEL extrapolation (in particular, when a threshold dose may not exist) or even a probabilistically derived benchmark dose distribution.

D.2.7 Other aspects relating to the dataset

Next to extrapolation, other important aspects of risk characterization are the adequacy of and confidence in the available data set and the nature of the effect. Most often, these aspects are dealt with in a qualitative way. When dealt with in a quantitative way, default values of 1 to 10 have been proposed (see Table D.1), but there is no agreed basis for these values. The US-EPA uses the term modifying factor to cover uncertainties other than the "extrapolation" uncertainty factors.

D.3 Overall uncertainty factor

Typically, the overall uncertainty factor is the product of the individual uncertainty factors, by assuming independency of the factors. It is to be realized that this multiplication is in general very conservative: when each individual uncertainty factor by itself is regarded as conservative, multiplication will lead to a piling up of conservatism. Hence, the more extrapolation steps are taken into account, the higher the level of conservatism.

Although not widely used up to now, a more recent development in risk assessment is the use of probability distributions and Monte Carlo simulation to obtain the overall uncertainty factor. By acknowledging that each uncertainty factor is uncertain and is best described by a lognormal distribution, propagation of the uncertainty can be evaluated by Monte Carlo simulation yielding a lognormal overall distribution for the combined uncertainty factor. This offers the possibility for a quantitative estimate of the probability that an adverse effect will occur in a certain population at the estimated exposure level. Moreover, the distribution of the overall uncertainty factor can be probabilistically combined with the distribution of the benchmark dose, as also the effect parameter is uncertain and is best described by a lognormal distribution.

Table D.1 — Examples of default uncertainty factors used in human health risk assessment

Uncertainty factors	WHO/IPCS (1987 [61], 1990 [62], 1994 [63], 1999 [64])	US-EPA (1993 [57])	ECETOC (2003 [3])	BAuA (1998 [2])
Interspecies	10	10	allometric scaling $(bw^{0,75})^a$ mouse 7, rat 4, monkey 2, dog 2	
Non-occupational				
— toxicokinetics	4,0			
— toxico-dynamics	2,5			
Occupational				allometric scaling $(bw^{0,75})^b$ mouse 7, rat 4, dog 2, monkey (marmoset) 4, monkey (rhesus) 2 (rounded figures)
Intra-species	10	10		
Non-occupational			5^c	
— toxicokinetics	3,16			
— toxico-dynamics	3,16			
Occupational			3	5^d
Duration of exposure		10		
System. eff./Local inhal. eff.			2/no (additional) uncertainty factor needed[e]	2/4

Table D.1 *(continued)*

Uncertainty factors	WHO/IPCS (1987 [61], 1990 [62], 1994 [63], 1999 [64])	US-EPA (1993 [57])	ECETOC (2003 [3])	BAuA (1998 [2])
— sub-chronic to chronic				2/4
— subacute to subchronic			6/no (additional) uncertainty factor needed[e]	6/12
— subacute to chronic			no (additional) uncertainty factor needed[e]	
Local dermal effects				
Route-to-route			no default proposed	
Oral to inhalation				1[f]
Oral to dermal				1[f]
Type of leading effect	1-10			
Dose-response curve				
Appropriate NOAEL			no (additional) uncertainty factor needed	
LOAEL to NAEL (NOAEL)	3-10	10	3[g]	3
Alternative	BMD	BMD	BMD	BMD
Confidence in database/ database adequacy	1-10			
Modifying factor		>0-10		
Overall factor	Multiplication of above figures	Multiplication of above figures	Multiplication of above figures[h]	Multiplication of above figures

[a] Allometric scaling (AS) not to be applied for inhalation route and for local effects; although AS does not completely account for interspecies differences, no additional assessment factor for 'residual' interspecies variability because that is largely accounted for in the assessment factor for intraspecies variability.

[b] Allometric scaling only to be applied for systemic effects, with doses in mg/kg bw (not for doses in mg/m^3 or mg/kg feed); not for local effects.

[c] No additional assessment factor for children needed but attention should be given to effects on developing organ systems, such as reproductive development in pre-puberty.

[d] After allometric scaling, this factor of 5 should be applied as combined assessment factor for intra- and interspecies extrapolation.

[e] For local effects below the threshold of cytotoxicity.

[f] Similar absorption by all routes is assumed (not necessarily 100 %).

[g] May need to be adjusted depending on dose spacing, shape and slope of dose-response curve and extent and severity of effect seen at LOAEL.

[h] By estimating the different parameters as typical values with central tendency, the product of these parameters reveals a central tendency estimate of the combined assessment factors. For evaluation of existing chemicals, this approach is modified as follows: an additional factor is used to account for the uncertainty of the assessment and the confidence in the database. By multiplication with this factor, the initial estimate is modified in terms of precaution. The resulting value represents the overall assessment factor.

Annex E
(informative)

Examples of testing methods

E.1 General

This Annex describes examples of existing test method for degradation, bioaccumulation, toxicity (acute, long term) and sediment adsorption of substances.

E.2 Test methods

Test methods relevant to this risk assessment are summarized in Tables E.1 to E.5.

Table E.1 — Examples of acute toxicity tests

Study	Reference
Oral toxicity	OECD 401 Acute oral toxicity
	OECD 420 Acute oral toxicity – Fixed dose procedure
	OECD 423 Acute oral Toxicity – Acute toxic class method
	OECD 425 Acute oral toxicity: Up-and-down procedure
Dermal toxicity	OECD 402 Acute dermal toxicity
Inhalation toxicity	OECD 403 Acute inhalation toxicity
Irritation/corrosion	OECD 404 Acute dermal irritation/corrosion
	OECD 405 Acute eye irritation/corrosion
	OECD 430 *In vitro* skin corrosion: Transcutaneous electrical resistance test (TER)
	OECD 431 *In vitro* skin corrosion: Human skin model test
	OECD 435 *In vitro* membrane barrier test method for skin corrosion
Skin sensitization	OECD 406 Skin sensitisation
	OECD 429 Skin sensitisation: Local lymph node assay

Table E.2 — Examples of repeat dose tests

Study	Reference
Oral toxicity	OECD 407 Repeated 28-day oral toxicity study in rodents
	OECD 408 Repeated dose 90-day oral toxicity study in rodents
	OECD 409 Repeated dose 90-day oral toxicity study in non-rodents
Dermal toxicity	OECD 410 Repeated dose dermal toxicity: 21/28-day study
	OECD 411 Subchronic dermal toxicity: 90-day study
Inhalation toxicity	OECD 412 Subacute inhalation toxicity: 28-day study
	OECD 413 Subchronic inhalation toxicity: 90-day study
Development toxicity	OECD 414 Prenatal development toxicity study
Reproduction toxicity	OECD 415 One-generation reproduction toxicity study
	OECD 416 Two generation reproduction toxicity study

Table E.2 *(continued)*

Study	Reference
Carcinogenicity	OECD 451 Carcinogenicity studies
Chronic toxicity	OECD 452 Chronic toxicity studies
Chronic toxicity/carcinogenicity	OECD 453 Combined chronic toxicity/carcinogenicity studies

Table E.3 — Examples of adsorption, distribution, metabolism and excretion studies

Study	Reference
Toxicokinetics	OECD 417 Toxicokinetics
Skin absorption	OECD 427 Skin absorption: *In-vivo* method
	OECD 428 Skin absorption: *In-vitro* method

Table E.4 — Examples of genotoxicity studies

Study	Reference
Genetic mutation	OECD 471 Bacterial reverse mutation test
	OECD 476 *In vitro* mammalian cell gene mutation test
	OECD 488 Transgenic rodent somatic and germ cell gene mutation assays
Chromosome aberration	OECD 473 *In vitro* mammalian chromosome aberration test
	OECD 474 Mammalian erythrocyte micronucleus test
	OECD 475 Mammalian bone marrow chromosome aberration test
	OECD 478 Genetic toxicology: Rodent dominant lethal test
	OECD 483 Mammalian spermatogonial chromosome aberration test
	OECD 484 Genetic toxicology: Mouse spot test
DNA damage	OECD 486 Unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo*

Table E.5 — Examples of neurotoxicity studies

Study	References
Delayed neurotoxicity	OECD 418 Delayed neurotoxicity of organophosphorus substances following acute exposure
	OECD 419 Delayed neurotoxicity of organophosphorus substances: 28 repeated dose study
Acute neurotoxicity	OECD 424 Neurotoxicity study in rodents

Annex F
(informative)

Examples of guidance for determining data quality

F.1 General

This Annex describes examples of existing guidance for determining toxicity data quality of hazardous substances.

F.2 OECD guidance on data quality evaluation

Manual for Investigation of HPV Chemicals. Chapter 3. Data Evaluation.

http://www.oecd.org/chemicalsafety/risk-assessment/36045203.pdf

F.3 EU guidance on data quality evaluation

European Chemicals Agency, 2011. Guidance on information requirements and chemical safety assessment Chapter R.4: Evaluation of available information. December 2011.

http://echa.europa.eu/documents/10162/13643/information_requirements_r4_en.pdf

Annex G
(normative)

Minimum required information for a risk assessment report

G.1 General

This Annex provides the minimum data/information requirement to be included in human health risk assessment report of substance submitted for application.

G.2 Information required for a report

These data and information are used for appropriate implementation of human health risk assessment.

When conducting risk characterization with the step-by-step approach described in Annex A, new data and information, excluding those used or obtained in the preceding process, are added as necessary according to the tier.

Any relevant significant data and information, other than the requirement listed in this Annex should be described in the risk assessment report.

Table G.1 — Minimum requirement information for the human health risk assessment report

Items	Data requirements	Tier 1	Tier 2	Tier 3
Applicant(s)	Name, address and point of contact for applicant(s)	X	X	X
	Name of manufacturer and plant location(s)	X	X	X
Identity of biocidally active substance	Common name and synonyms.	X	X	X
	Chemical name (IUPAC)	X	X	X
	CAS number and other registry numbers	X	X	X
	Molecular and structural formula	X	X	X
	Molecular mass	X	X	X
	Methods of manufacture and purity of substance and identity of material(s) and precursor(s)	X	X	X
	Identity of impurities and additives	X	X	X
Physical and chemical property	Molecular weight	X	X	X
	Melting point, boiling point and relative density	X	X	X
	Vapour pressure, flash-point and surface tension, if applicable	X	X	X
	Physical state and colour	X	X	X
	Water solubility (effect of pH and temperature)	X	X	X
	Thermal stability and decomposition product(s).	X	X	X
	n-octanol/water partition coefficient (effect of pH and temperature)	X	X	X

GHS: United Nations (2013) Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Fifth revised edition, New York and Geneva, 2013

X Minimum data required.

(X) Data required as appropriate. (See Annex A.)

Table G.1 *(continued)*

Items	Data requirements	Tier 1	Tier 2	Tier 3
Identity of representative product	Product name	(X)	(X)	(X)
	Content of biocidally active substance(s)	X	X	X
	Envisage user	X	X	X
	Application method	X	X	X
Analytical methods for detection and identification	Analytical methods, recovery rates and limits of determination of pure substance, isomers, impurities, additives and degradation products in/on			
	— animal body tissue and food	X	X	X
Toxicological and metabolic studies for human	Related data for — acute toxicity, — metabolism studies, — repeated dose toxicity, — long-term toxicity, — mutagenicity studies, — carcinogenicity studies, — reproductive studies, — neurotoxicity studies, — metabolism studies, — medical data, and — toxic effects on mammalians, including livestock, pets and human, where necessary.	(X)	(X)	(X)
Classification and labelling	Label elements (classification category, symbol, hazard statement and precautionary statements) for health hazards in GHS classification of biocidally active substance.	X	X	X
Risk characterization	Uncertainty factors and quantitative statement of these level	X	X	X
	MOE of biocidally active substance	X	X	X
Summary		X	X	X

GHS: United Nations (2013) Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Fifth revised edition, New York and Geneva, 2013

X Minimum data required.

(X) Data required as appropriate. (See Annex A.)

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