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Acute Inhalation Toxicity in Quantitative Risk Assessment – Methods and Procedures

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In the Netherlands, quantitative risk assessment (QRA) is used for land-use planning purposes for external safety. Under Dutch legislation, the individual risk and societal risk of activities involving hazardous substances must be calculated using a standardized method.
One of the effects considered in the QRA method is acute inhalation toxicity. In order to estimate the number of deaths as a result of acute exposure to toxic chemicals, probit functions are used. A lethality probit function describes the lethality rate in an exposed population as a function of any combination of the exposure concentration and exposure duration. Probit functions are derived from animal studies according to a specified method.
In 2008, the Dutch Ministry of Environment commissioned a 5-member scientific expert panel, charged with (1) reviewing newly derived or revised probit functions and (2) developing and maintaining robust protocols and criteria necessary to produce these probit functions. After scientific approval by the expert panel, the Ministry will decide whether or not a probit function will be formally implemented for use in QRAs. This decision is primarily based on the results of an analysis of the consequences (in terms of individual and societal risk) of implementation.
Between 2008 and 2012, the existing method for derivation of probit functions was thoroughly revised by the expert panel. Major revisions include higher demands on the quality of inhalation toxicological data, and the consideration of data on (non-)lethal effects in humans, if these are available.
Since its inception in 2008, the expert panel has reviewed probit functions for 46 substances, including 37 new and 9 revised. As part of the standard procedure, draft probit documents are published for public review before being discussed by the expert panel. On some occasions this has resulted in discussion between the expert panel and third parties. In general, the revised method yields slightly more conservative probit functions than the former method, but the implementation of a revised probit function will have significant consequences in QRAs for a limited number of substances only.
As of January 2013, no new or revised probit functions have been formally implemented. However, new probit functions that have been approved by the expert panel are used in QRAs.

1. Introduction

In the Netherlands, quantitative risk assessment (QRA) is used for land-use planning purposes. Under Dutch legislation (Ministry of VROM, 2004), the individual risk and societal risk of activities involving hazardous substances must be calculated using a standardized method.
One of the effects considered in the QRA method is acute inhalation toxicity. In order to estimate the number of deaths as a result of acute exposure to toxic chemicals, probit functions are used. A lethality probit function describes the lethality rate in an exposed population as a function of any combination of the exposure concentration and exposure duration.
A probit function is expressed as

$$\mathrm{Pr} = -a + b \times \ln\left(C^n \times t\right) \tag{1}$$

where Pr is probit; a, b and n are constants; C is concentration; t is exposure duration.

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Probit functions are derived from animal studies according to a specified method (Ruijten et al., 2013). For a number of substances, probit functions have been derived in the past, and have been implemented in the QRA method (RIVM, 2009). When necessary, new probit functions may be derived (e.g. when a QRA requires data on a substance for which no probit functions is available), or existing probit functions may be revised (e.g. when new toxicological data become available). The selection of substances for derivation of probits is the responsibility of the Ministry of Environment.
Since 2008, new procedures concerning the derivation, evaluation and implementation of probit functions have been developed and implemented. This paper will briefly describe the procedures, and will provide the current state of affairs with regard to the derivation, evaluation and implementation of probit functions.

2. The expert panel

In 2008, the Netherlands' Ministry of Environment (VROM) commissioned an independent 5-member scientific expert panel on probit functions. Members of the panel are from different fields of work (industry, consultancy, governmental) and have a background in toxicology, most of them with extensive experience in inhalation toxicology.
The mission of the expert panel is:

- To advise the Ministry about the toxic properties of chemicals, particularly to provide the best possible support for a probit function based on current scientific understanding.
- To develop, maintain and publish robust protocols and criteria necessary to produce the aforementioned advice, in a transparent and reproducible manner.

3. Method for derivation of probit functions

The original method for the derivation or revision of probit functions has been described in volume 1, part 4 of the Netherlands' Publication Series on Dangerous Substances (Ministry of VROM, 2005). Since 2008, the method has been revised by the scientific expert panel, in order to meet current scientific standards and insights. The revised method (Ruijten et al., 2013) makes use of various assessment factors, to account for e.g. data quality, sensory irritation, and inter- and intra-species variability. Major revisions to the method as compared to the previous version include the following:

- The revised method puts higher demands on the quality of inhalation toxicological data.
- The derivation of probit functions based on 'life threatening values' (LBW) is no longer allowed.
- The derivation of probit functions via LC_{50} values (LC_{50} is a measure of toxicity) and the old flow-chart based on allometric scaling is not allowed.
- The procedure to raise the LC_{50} value as point of departure when data from two or more animal species is available has been dropped.

A number of general assumptions and basic principles underlie the derivation and application of probit functions:

- Non-lethal health effects are not considered.
- Probit functions are intended to predict the lethality following acute inhalation exposure.
- The probit functions assume an 'average' population, including susceptible subjects.
- The probit functions assume that the exposed persons are not protected by personal protective equipment or shelter in place, nor that they receive medical treatment following exposure.
- Possible lethality from delayed effects such as carcinogenicity or reproductive toxicity is not taken into account.
- Possible lethality following secondary exposure is not taken into account.
- Possible secondary lethality from other causes than acute toxicity is not taken into account.
- Exposure time is not limited; the possibility of an evacuation is not included in the QRA.

Since many datasets do not meet the quality criteria set by the expert panel on probit functions, the expert panel has chosen to use the existing data to its limits and compensate for the uncertainty introduced due to substandard datasets by applying additional assessment factors, rather than not deriving a probit function for those substances. A general assessment factor for overall study quality may be applied when, for example, the value for n and/or the LC_{50} cannot be determined with sufficient certainty (e.g. if data are available for just 1 duration of exposure), or when the probit function is based on the toxicity of a hydrolysis product, but it is uncertain if the particular hydrolysis products toxicity suffices to predict the parent compound's toxicity. In such cases an additional assessment factor of 2 or 3 can be applied. The revised method is intended to be a 'living' document, and may be amended by the expert panel at any time based on new scientific insights. Figure 1 outlines the method to derive a probit function from animal toxicity data.

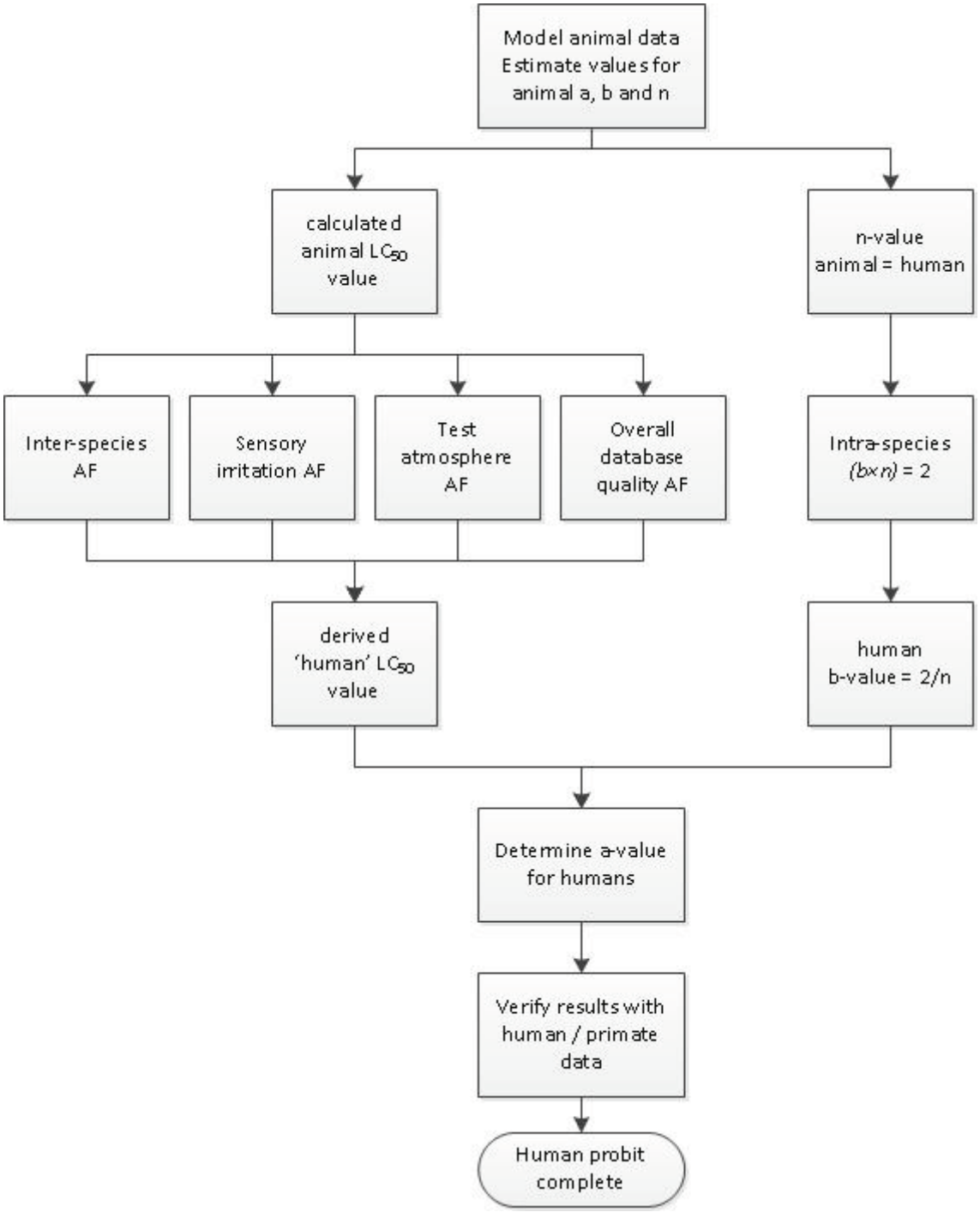

Figure 1: Flowchart for developing a human probit function from animal lethality data (AF = assessment factor)

4. Procedures for derivation, evaluation and implementation of probit functions

4.1 Introduction

Before a probit function is implemented (i.e. becomes part of the QRA method and as such must be used in QRA calculations), a process of derivation, evaluation and implementation is followed. A new probit function may be derived for a substance currently without a formalized probit function, or an existing probit function included in RIVM (2009) may be revised. Such a revision may be initiated when, for example, new toxicological data have become available.

There are two possible starting points for the procedure: a “public” and a “private” route. The “public” route is intended for substances for which the implementation of a probit function is considered of general interest. For these substances, the probit function is derived under the authority of RIVM. The “private” route is intended for any other substance, for which a party (e.g. industry) is interested in having a probit function implemented. The party can produce a substance document and derive a draft probit function.

4.2 Drafting of the substance document
The substance document is drafted according to the designated method (Ruijten et al., 2012) and using a prescribed template. The document includes a clarification of the steps leading to the derivation of the draft probit function. The substance document and any relevant background information including references, is submitted to the technical secretariat of the expert panel at RIVM.

4.3 Publication and public comment
After a completeness check, the document is assigned the status “proposed”, and is published on a designated website for a 6-week public comment period. Interested parties may submit written comments on the derivation of the probit function.

4.4 Evaluation by the expert panel
Proposed probit functions and any public comments received are evaluated in a meeting of the scientific expert panel. The discussion focuses on (1) assessment of the quality of the substance document and the underlying data, and (2) the derivation of the probit function. The evaluation by the expert panel is strictly scientific and does not account for e.g. economic or policy consequences of an eventual implementation of the probit function. A proposed probit function may be either approved or rejected by the expert panel. In case of conflicting opinions between expert panel members, decisions are taken by means of majority voting. Approval of a probit function results in its status being raised from “proposed” to “interim”, and publication of the “interim” substance document.

4.5 Consequence analysis and implementation
After scientific approval by the expert panel, the Ministry will decide whether or not a probit function will be formally implemented for use in QRAs. This decision is primarily based on the results of an analysis of the consequences (in terms of individual and societal risk) of implementation. A general procedure for such an analysis is provided in RIVM (2011).The Ministry will not question the scientific advice of the expert panel.
If a probit function is implemented, its status is raised from “interim” to “established”, and the final substance document is published.

5. Results achieved and current state of affairs

5.1 Results achieved
Since its inception in 2008, the expert panel has revised the method for derivation of probit functions. The method meets current scientific standards and insights; however, the expert panel remains open to any suggestions for further improvement. Since 2008, the expert panel has reviewed probit functions for 46 substances, including 37 new and 9 revised. Of these, 36 probit functions have been approved by the expert panel; 6 have been rejected, primarily for lack of data of sufficient quality. A number of proposed probits is still subject to discussion. An up-to-date status overview is provided in Table 1.

5.2 Consequence analysis
Of the 36 probit functions approved as of January 2013, 24 have been analyzed for the consequences of their eventual implementation in QRAs. In general, the revised method yields slightly more conservative probit functions than the former method, mainly because of the stricter requirements on data quality. In QRAs, this may be reflected in terms of increased risk, such as larger individual risk contours around an establishment, or an exceedance of the orientation value for societal risk. For most substances, the consequences are limited: either the increase in risk is negligible, or the increased risk has no implications (because, for example, there are no additional vulnerable objects within the new 10^{-6} individual risk contour). For a number of substances, however, implementation of the revised probit function may have considerable consequences. For example, the probit function for hydrogen chloride has become more conservative. Since hydrogen chloride is modeled as a toxic combustion product in the QRA method for warehouse fires, implementation of the revised probit function may impact the risk level for warehouses.

5.3 Implementation of probit functions
As of January 2013, no new or revised probit functions have been formally implemented. However, newly derived probit functions (for substances that do not yet have a formal probit function) that have been approved by the expert panel can be used in QRAs.

Table 1: Substances for which a probit function has been derived or revised

Substance	Status of the probit function (January 2013)
1,2-dichloroethane	interim
acetone cyanohydrin	interim
acetonitrile	interim
acrylonitrile	proposed
allyl alcohol	interim
allylamine	interim
allyl chloride	proposed
ammonia	proposed
arsine	interim
benzyl chloride	interim
boron trichloride	interim
boron trifluoride	interim
chloroacetaldehyde	interim
dichlorosilane	interim
dimethylamine	interim
dimethyl sulfate	interim
epichlorohydrin	interim
ethyl chloroformate	interim
ethyleneimine	interim
fluorine	interim
formaldehyde	interim
phosphine	interim
phosphorus oxychloride	proposed
phosphorous trichloride	proposed
hydrazine	interim
methacrylonitrile	proposed
methylamine	interim
methyl chloroformate	interim
methyl mercaptan	interim
n-butyl acetate	interim
oxalonitrile	interim
propylamine	interim
propyleneimine	interim
nickel carbonyl	interim
tetrachlorosilane	interim
toluene diisocyanate	interim
trichlorosilane	interim
triethylamine	interim
trimethylamine	interim
hydrogen chloride	interim
hydrogen cyanide	interim
hydrogen sulfide	interim
sulphur trioxide	proposed
sulphuric acid	proposed

6. Conclusions

Lethality probit functions are an important element of the QRA method in the Netherlands. Between 2008 and 2012 several improvements were made with regards to the derivation, evaluation and implementation of probit functions. The method for derivation of probit functions was updated to current scientific

standards, and new prodedures were implemented. A substantial number of new or revised probit functions was produced. In general, the revised method yields slightly more conservative probit functions than the former method, but the implementation of a revised probit function will have significant consequences in QRAs for a limited number of substances only. For a number of substances, publication of the substance document led third parties to provide comments and/or additional toxicological information. In a number of cases (e.g. hydrogen cyanide, ammonia), this has resulted in meaningful discussion. Most notably, the probit function for hydrogen chloride was modified as a result of comments and additional toxicological information received from the chemical industry. In addition, this specific case has led the expert panel to implement an additional element into the method for derivation of probit functions, which takes into consideration data on lethal or non-lethal responses in humans and other primates, should such data be available. In order to achieve even broader acceptance of the method for derivation of probit functions, an international expert review of the method is planned in the first half of 2013.

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