# A revised method for assessing acute inhalation toxicity in quantitative risk analysis

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Quantitative risk analysis (QRA) is an important instrument in land-use planning in the Netherlands. It provides insight into the risks of the use, transport and storage of dangerous substances. In a QRA, probit functions are used to estimate the proportion of fatalities in an exposed population following (accidental) exposure to toxic chemicals. A probit function for acute inhalation toxicity of a chemical describes the probability of death in an exposed population as a function of any combination of the exposure concentration and exposure duration. Probit functions are derived from animal toxicity data. In the early 2000s, the Ministry of Infrastructure and the Environment initiated the unification of methods, procedures and information sources for QRAs. As part of this unification process, the probit functions and the scientific and administrative procedures used to derive probit functions were reviewed and updated. This paper describes the process resulting in the publication of the method for the derivation of probit functions. The method was thoroughly revised by the Netherlands' Expert Panel on probit functions. In order to further improve the scientific basis, validity, appropriateness and acceptance of the method, an international invitational meeting was convened, bringing together renowned international experts in the field of risk assessment for acute airborne exposures. The meeting resulted in a set of recommendations, that were incorporated in the method which was published in July 2015. After introducing the basic philosophy of deriving a probit function, the method describes in detail the interpretation and use of animal data and the derivation of the probit function. Use of the method results in a transparent, verifiable, robust and valid, technical substance document that provides a consistent, uniform approach and quality.

Keywords: quantitative risk analysis, QRA, land-use planning, acute inhalation toxicity, probit

## Introduction

### Use of QRA in land-use planning

In The Netherlands, Quantitative Risk Analysis (QRA) is used to support decision making on land use planning and the acceptability of risk, in relation to developments for a company or in the area surrounding an establishment or transport route. The criteria for assessing risks for a large number of categories of establishments are set in the External Safety (Establishments) Decree (Bevi) (Ministry of VROM 2004).

In order to be able to use the results of a QRA for decisions, these results must be verifiable, reproducible and comparable. Consequently, QRAs must be carried out based upon the same assumptions, models and basic information. These are described in detail in the Reference Manual Bevi Risk Assessments (RIVM 2009), which together with the SAFETI-NL calculation package represents the calculation method for carrying out a QRA as part of the Bevi. The use of this calculation method is mandatory for determining location-specific risk and societal risk for the establishments covered by the Bevi.

### QRA method and effects concerned

The calculation method as described in the Reference Manual provides insight into the expected number of acute fatalities in an accident involving dangerous substances. In the method, three types of acute, (potentially) lethal effects are concerned: overpressure, heat radiation and inhalation toxicity. For each effect, a specific calculation approach is prescribed based on scientific models and assumptions, in order to estimate the number of fatalities in the exposed population.

For the model-based estimation of lethality by inhalation of toxic substances, the use of *probit functions* is prescribed.

### Probit functions for acute inhalation toxicity

A probit function (a statistical term combining *probability* and *unit*) indicates the relationship between the concentration of a substance, the exposure time and the effect on (in this case) human beings:

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

in which Pr = probit value; $a$, $b$ and $n$ are substance-specific constants; $C$ = concentration and $t$ = exposure time.

This way, a probit function for a substance can be used to estimate the percentage of fatalities in the direct vicinity of an accident caused by exposure to the toxic substance, in any random combination of concentration and exposure time (see Figure 1 for an example of the concentration-time-response relationship). Probit functions are based on toxicological information from animals which are converted into exposure-response relationships for humans. The method is described in more detail in the next section.

Probit functions have already been formally determined for several tens of substances, and included in the Reference Manual Bevi Risk Assessments. For substances with no probit function available, a probit function can be derived, evaluated and implemented according to a fixed procedure.

## Derivation and evaluation of probit functions

### Introduction

Up to 2005, the Netherlands' *Committee for the Prevention of Disasters caused by hazardous substances* (CPR) was responsible for the evaluation of probit functions for acute inhalation toxicity. When the CPR ceased to exist in 2005, a body overseeing the scientific basis of the probit derivation method and procedures was lacking. In 2008, the then Ministry of Housing, Spatial Planning and the Environment therefore appointed a scientific Expert Panel on probit functions. The mission of this Panel is:

1. To advise the Ministry about the toxic properties of chemicals and, particularly, to provide the best possible support for a probit function based on current scientific understanding.

2. To develop, maintain and publish the robust protocols and criteria necessary to produce the advice mentioned under 1., in a transparent and reproducible manner.

Since 2014, the Panel operates under authority of the Netherlands' National Institute for Public Health and the Environment RIVM. The Expert Panel currently consists of 6 members from both public and private organisations.

### Procedure for derivation, evaluation and implementation

After its inception, the Expert Panel first set out to develop standard procedures for the derivation, evaluation and implementation of probit functions. Before a probit function can be included in the Reference Manual, a step-by-step process must be followed (see Figure 2).

- *Derivation*. The derivation of a probit function takes place using an established method based on information from literature. The derivation of a probit function is described in a technical document, which is drafted according to a template provided. This results in a transparent, verifiable, robust and valid, technical substance document that provides a consistent, uniform approach and quality.

- *External public comment*. After a check for completeness, concept substance documents and the probit functions are assigned the status 'proposed'. The documents are published on the RIVM website in order to provide interested parties with the opportunity to comment or provide additional information. Interested parties are informed of the publication of new substance documents.

- *Evaluation*. The proposed probit functions and any comments received are scientifically evaluated by the Expert Panel. The Expert Panel evaluates whether a proposed probit function has been derived correctly and in conformity with the method for the derivation, thus assessing its validity. The Expert Panel provides advice based on scientific grounds about proposed probit functions. The Expert Panel's approval of a probit function results in a document and probit function with the status 'interim'.

- *Consequence analysis*. After the conclusion of the scientific process, a consequence analysis is carried out under the direction of RIVM. The technical consequences in dealing with a new probit function are mapped out, and the societal impact of the possible implementation of a probit function in the calculation method is considered. In conjunction with the industry, RIVM draws up a plan to ensure that all stakeholders involved receive the opportunity to provide input for the process and the execution of the analyses.

- *Implementation*. RIVM presents the scientific advice from the Expert Panel and the results of the consequence analysis to the Ministry of Infrastructure and the Environment. The Ministry weighs the societal feasibility and affordability and establishes whether, and if so, in what time frame and under which conditions a probit function will be implemented and fits into the legally prescribed calculation methods. By the compulsory prescription of a probit function, the Ministry of Infrastructure and the Environment raises the status of a probit function to 'established'. The establishment of a probit function ultimately results in an update of the Reference Manual.

In the near future, step 2 and 3 of the process described above may be performed in reverse order, meaning that probit functions will be evaluated by the Expert Panel before being published for public comment.

## Revision of the method for derivation of probit functions

### Introduction

As mentioned before, the Expert Panel is tasked to develop and maintain the method to produce probit functions in a transparent and reproducible manner. Since 2008, the Expert Panel has worked on updating the existing method for derivation of probit functions to a state-of-the-art document, using valuable input from third parties, including industry and scientific experts, in the process. This section describes the process that resulted in the publication of the method in 2015.

### Revision of the 'Green Book'

The method for derivation of probit functions was formerly described in Chapter 4 of PGS1, or the 'Green Book' (Ministry of VROM 2005). In 2008, the Expert Panel started to revise and update the Green Book approach to current scientific standards. A first list of amendments to the method was drafted and published by the Expert Panel in 2008. An important amendment to the method was the much higher demands on the quality of inhalation toxicological data before acceptance as a 'point of departure' for derivation of the probit function. Further, the derivation of probit functions based on emergency

response 'intervention values' was no longer allowed; the derivation of probit functions via $LC_{50}$ values and the old flow chart based on allometric scaling was not allowed; and the procedure whereby the $LC_{50}$ value as a point of departure is multiplied by a factor 2 when data from two or more animal species is available, was no longer considered to be valid.

These amendments were to be taken into account when deriving new probit functions. For each newly derived probit function, extensive technical documentation describing the derivation of the probit function was published on the RIVM website, providing insight into the amended method and giving third parties the opportunity to comment on the proposed derivation. Between 2008 and 2010, some 30 probit functions were derived according to the revised approach, and evaluated and approved by the Expert Panel. No significant comments or additional information were received from third parties.

## Third party comments

In 2010 and 2011, probit functions were derived and published for a number of high profile chemical substances, which led to significant discussion concerning the method as amended by the Expert Panel, and the procedures for derivation, evaluation and implementation of probit functions. In particular, much interest was generated among third parties by the revision of the probit functions for hydrogen chloride, hydrogen cyanide and ammonia. All of these chemicals are used in large quantities at chemical plants in the Netherlands, implying that a change in the probit values used in the QRA could have a significant impact on the calculated risk for these plants. Even though the probit functions at this stage were still under review and not yet formally implemented, unrest was generated. Comments were submitted by industry, as well as a number of consultancies and competent authorities. It appeared that not only the method for derivation of probits was subject to discussion, but many parties were unaware of the procedures in place, or the status of the probit functions published.

On a number of occasions, the Expert Panel invited industry representatives to its meetings to provide oral clarification of their comments. This led to some incidental modifications to the probit functions, because e.g. additional toxicological information had been provided.

In order to address the concerns raised collectively, it was decided to organize a meeting for stakeholders and other interested parties. At this one-day meeting, which took place in 2012, the Expert Panel, the chemical industry, the Ministry of Housing, Spatial Planning and the Environment, competent authorities and consultancies performing the QRA calculations were all present. The ministry provided more insight into its policy, the procedures and the philosophy behind the derivation and implementation of probit functions. The industry was offered the opportunity to express their concerns and to clarify its stance regarding the method for derivation of probit functions, identifying some major discussion items. There was consensus that, since most participants of the meeting lacked the necessary toxicological background, another meeting would be held, dedicated exclusively to expert discussions on the method.

## International expert meeting

An invitational workshop to review the method for derivation of probit functions was held from 24-26 September 2013. The objective of the workshop, jointly organized by the Expert Panel, the Dutch chemical industry and RIVM, was to improve the scientific basis, validity, appropriateness and acceptance of the current method (as modified by the Expert Panel) to derive probit functions for acute lethality. Renowned international experts in the field of risk assessment of acute airborne exposures were brought together to discuss strengths, weaknesses and opportunities to improve the revised method.

The intended outcome of the workshop was a set of recommendations to the Expert Panel for improvement of the method. Recommendations should ideally be:

- Practical and feasible with reasonable data requirements (minimizing the need to generate new data);
- A clear improvement over the existing method, both from a scientific and societal point of view;
- Philosophically and practically compatible with other risk assessment methodologies (so far as these are applicable to risk assessment of incident scenarios) as far as possible, particularly those generally applied in Europe.

In preparation of the workshop, the invited experts reviewed the current method and nominated subjects for discussion at the workshop. Six subjects were selected for discussion, including data quality assessment and selection of animal data, inter-species extrapolation (variability between experimental animal species and man), and intra-species variability (variability within the human population).

The general feedback from the participants, both in writing and at the meeting, was that the draft approach was felt to be one of the most elaborated and scientifically sound approaches for deriving probit functions known to the participants (Ter Burg 2013). The approach as a whole received general support, although a number of specific issues were identified for discussion and evaluation. The meeting resulted in a set of recommendations to the Expert Panel. A number of recommendations implied follow-up work for the Expert Panel.

## Publication of the method for derivation of probit functions

Between 2013 and 2015, the Expert Panel finalized the method for derivation of probit functions, which was published in July 2015 (Ruijten 2015). The results of the discussion at the international meeting were used to further improve the method. As a result, the toxicological evaluation of data and the application of quality criteria to toxicological data became more prominent elements of the derivation process.

After introducing the basic philosophy of deriving a probit function, the method describes in detail the interpretation and use of animal data and the derivation of the probit function. Stepwise guidance is provided for drafting a technical substance

document. This results in a transparent, verifiable, robust and valid document that provides a consistent, uniform approach and quality. The science and assumptions underlying the method are described in detail in the method document. Authors of probit technical substance documents are encouraged to follow the formats provided, and to use the exposure-response assessment approach presented in the method. The Expert Panel will consider a sufficiently justified deviation from this approach.

Many datasets do not meet the quality criteria set by the Expert Panel. Rather than not deriving a probit function for those substances, the Expert Panel has chosen to use the existing data to its limits and to appropriately compensate for the introduced uncertainty.

## Summary and conclusions

The method for derivation of probit functions used in the Netherlands was updated and revised by the Expert Panel on probit functions. As a starting point, a list of amendments to the existing method was drafted by the Panel. Several probit functions were derived according to the amended method. Publication of draft probit functions for a number of high-profile chemicals led to discussions with stakeholders regarding the derivation method and the procedures for derivation, evaluation and implementation. In order to address the issues raised with regard to the method, the Expert Panel and the chemical industry initiated an international expert meeting, with the aim of further improving the scientific basis, validity, appropriateness and acceptance of the method. Recommendations from the expert meeting were incorporated in the method, which was published in July 2015. The result of this process, involving all relevant stakeholders, is a state-of-the-art, internationally reviewed methodology for derivation of probit functions for acute inhalation toxicity, to be used in quantitative risk analysis.

The Expert Panel is aware that many scientific issues remain unresolved, but also that with time and future research, new scientific insights can be obtained and implemented. The method is therefore considered a ‘living document’ that may be discussed and amended at any time based on these insights, keeping it the best available, and widely accepted, method.

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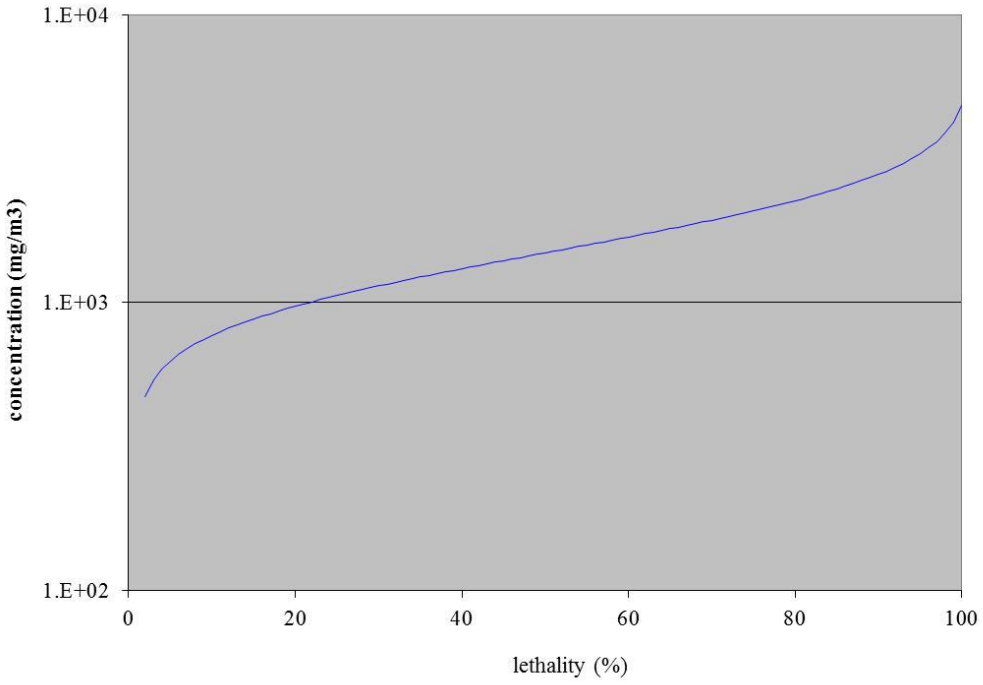


**Figure 1. Example of a lethality probit function at a given exposure time**


**Figure 2. Procedure for derivation, evaluation and implementation of probit functions**