# Probit functions for selected chemicals based on AEGL-3 values

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## Summary

Leaks of volatile and highly toxic chemicals can form gas clouds, which may be transported long distances by the wind before the turbulence dilutes the gas cloud to harmless concentrations. Dispersion models obtained at FOI describe the distribution of chemicals in the environment after, for example, an accident or fire. To interpret how various emission scenarios / events described in these dispersion models may affect the population there is a need to estimate response rates (percental individuals with detrimental health effects), preferably at different levels of injury.

In order to estimate the response rate, good quality data from chemical exposure is required at different exposure periods and with relevant endpoints. In this report, we have used AEGL (Acute Exposure Guideline Levels) guideline values because they are scientifically based, open access, and describe effects and response rates at multiple exposure durations up to eight hours of exposure. The AEGL values are based on an average population and include both healthy and sensitive individuals.

The probit function describes the relationship between the exposure period, the chemical concentrations in air, and the response rate. Data from dispersion models concerning chemical concentration in air and exposure period can be used in chemical specific probit functions to estimate the response rate in the population. Here we have calculated regression coefficients for the probit function based on AEGL-3 values. We have included several common and / or toxic chemicals found in industry and in smoke from fires. It also includes chemicals that are classified as weapons of mass destruction/chemical warfare agents.

To validate the regression coefficients, we compare the AEGL-3 values for the chemicals with our calculated values based on probit functions derived via AEGL-3 values. For most chemicals there is a good fit between our calculated values and the corresponding AEGL-3 values. We have calculated the chemical concentration in air with a defined exposure time and response rate using the probit functions derived by RIVM and via AEGL-3, respectively. In general, the calculated chemical concentrations derived via the probit functions from RIVM were higher than the chemical concentrations calculated via the probit functions based on AEGL-3, i.e. AEGL-3 estimates that life-threatening effects may occur at lower chemical concentration of exposure. This can be explained by the use of different scientific studies, differences in the interpretation of toxicity data, and the use of different assessment (safety) factors to extrapolate / translate results from animal to human, and if sensitive individuals are considered or not. We have not analysed the contribution of these factors. In conclusion, we suggest that the probit functions derived by RIVM are used to calculate response rates of the general population where there is a risk of lethal exposure after a chemical emission. Furthermore, probit functions based on AEGL-3 are recommended by us to be used for chemicals where probit functions have not been published by RIVM.


Keywords: Risk area assessments, probit function, toxic industrial chemicals, gases from smoke and fire, chemical warfare agents.

# Sammanfattning

Läckage av flyktiga och högtoxiska kemikalier kan bilda gasmoln, som ibland kan transporteras långa avstånd med vinden innan turbulensen späder ut gasmolnen till ofarliga koncentrationer. Spridningsmodeller som tas fram vid FOI beskriver fördelningen av kemikalier i omgivningen efter t.ex. en olycka eller brand. Med dessa beräkningar som grund kan man därefter genomföra skadeutfallsberäkningar av uppskattad skaderisk för allmänheten vid olika exempel på utsläppsscenarier/-händelser. Denna rapport är helt omarbetad mot tidigare rapporter framtagna av FOI/tidigare FOA. I tillägg har fyra nya kemikalier lagts till då de, liksom de tidigare industrikemikalierna, kan återfinnas i brandrök.

För att kunna göra skadeutfallsberäkningar behövs data av god kvalitet från kemikalieexponering med olika koncentrationer vid olika tidpunkter och med tydliga mätbara effekter. I detta arbete har vi använt AEGL (Acute Exposure Guideline Levels) riktvärden eftersom de är vetenskapligt baserade, är öppet tillgängliga, beskriver effekter och skadeutfall vid flera tidpunkter och är utformade och beräknade utifrån en genomsnittlig population, d.v.s. både för friska och känsliga individer.

Probitfunktionen beskriver förhållandet mellan exponeringstiden, koncentrationerna i luften och skadeutfallet (andel personer som riskerar skadliga hälsoeffekter). I denna rapport har vi tagit fram regressionskoefficienter för probitfunktionen baserat på AEGL-3 värden för utvalda ämnen så att skadeutfallsberäkningar kan göras vid spridningsscenarier vid valfria tider upp till åtta timmars exponering. Metoden att ta fram regressionskoefficienten β kommer ifrån RIVM (Rijksinstituut voor Volksgezondheid en Milieu (Statens institut för folkhälsa och miljö), Nederländerna. För att validera probitfunktionen så jämfördes våra beräknade kemiska koncentrationer i luft med motsvarande AEGL-3 värden. För de flesta kemikalier överensstämmer våra beräknade koncentrationer relativt väl med AEGL-3. Vi jämför även probitfunktionerna framtagna via AEGL-3 med probitfunktioner framtagna av RIVM. För de flesta kemikalierna beräknar probitfunktionen baserad på AEGL-3, vid en given exponeringstid och skadeutfall, att risk för allvarlig skada sker vid lägre koncentrationer i luft jämfört med RIVM:s probitfunktion. Skillnaderna kan bero på att data baseras på olika studier, bedömer toxicitetsdata på olika sätt samt använder olika säkerhetsfaktorer för att extrapolera/ översätta resultat från djur till människa. I denna rapport har vi inte analyserat vad dessa variationer beror på för de enskilda kemikalierna. Sammanfattningsvis, föreslår vi att probit funktioner beräknade av RIVM används i första hand för att beräkna skadeutfall där det finns risk för dödlig exponering efter ett kemikalieutsläpp för en genomsnittlig befolkning. Vidare föreslår vi att probitfunktioner baserade på AEGL-3 används för kemikalier där RIVM inte har publicerat probitfunktioner.

Nyckelord: Skadeutfallsberäkningar, probitfunktion, riskområde, industrikemikalier, brandgaser, nervgaser.

# Content

# Objectives

The purpose of this report is to provide the values of the regression coefficients alpha (α) and beta (β), which are used in the probit function. The probit function has been selected because it is a straightforward model and is internationally common in assessment of human response rates (percental individuals at risk for detrimental health effects) following an acute chemical inhalation exposure. The probit function can be used when interpreting acute health risks in a scenario or after an actual chemical emission to air illustrated by dispersion models developed at FOI.

# Introduction

Release of chemicals into air may occur either accidentally for instance during production, storage, transport and handling or as a consequence of fire or deliberate release. In case of a chemical release, the chemical can spread to surrounding areas with risk of exposure to people in the vicinity. Release of volatile chemicals may form gas clouds, which sometimes can be transported long distances by the wind before turbulence dilutes the gas cloud to harmless concentrations.

Risk assessment of chemical hazards should include the negative health effects in the population in relation to the exposure situation, for instance period of exposure and the chemical concentration that reaches the body e.g. the respiratory tract. Such data may be used to interpret the risk of negative health effects in mathematical models describing the dispersion of chemicals in air.

## Risk of negative health effects in relation to levels of chemicals in air and exposure period

Acute exposure reference values (AERVs) are threshold or guideline levels for airborne chemicals for predefined levels of toxicity at multiple exposure periods [1]. The AERVs predict the risk of negative health effects of the general population following a single inhalation exposure and are useful, for instance, in emergency response and land-use. AERVs are generally extrapolated from experimental animal toxicity studies using relevant exposure routes, most often inhalation studies. Experimental human data are sometimes available for low exposure levels leading to transient and mild effects or no effects. In cases where human data are available from accidental poisoning, it is difficult to estimate the magnitude of exposure such as duration and concentration in air. Even interpreting the degree of symptoms and diagnostics is difficult due to individual variation, and some symptoms may be delayed e.g. pulmonary edema. Therefore, most data originate from animal studies, whereas data from human exposure can provide supportive information. A complete and concurring set of toxicological data with multiple exposure durations is important for deriving AERVs.

There are several AERVs such as AEGL[1], DTL[2], ERPG[3], DIV[4] and VSTAF[5]. At present, there is no general European method for risk assessment or risk management for acute chemical releases in incident scenarios. Between the different AERVs there are variations in dose response modelling, usage and interpretation of toxicological endpoints, and the level of protection for subpopulations such as sensitive individuals as determined by the criteria for setting assessment (safety) factors. The AERVs mentioned here consist of two to four tier levels representing different levels of health effect.

AEGL was chosen for this report since the methodology is scientifically based, the underlying data and interpretation of data is publically available and the data is generated for the general population including sensitive individuals at normal activity (2). Another advantage with AEGL is that there are values following single exposures to airborne chemicals for several exposure periods (10 min, 30 min and 1, 4, and 8 h).

The three tier levels of AEGLs are:

- AEGL-1. Individuals could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.
- AEGL-2. Individuals could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.
- AEGL-3. Individuals could experience life-threatening health effects or death.

The high exposure levels (AEGL-2 and AEGL-3) are based on animal experimental data whereas for the low exposure level (AEGL-1) there may be supporting data based on human subjects. The animal data have been scaled to levels for human exposure using assessment (safety) factors that take into account toxicodynamics (how the chemical affects the body) and toxicokinetics (what the body does with the chemical).

## Modelling response rates at different exposure scenarios

In toxicology, the probit function can be used to describe the relationship between chemical concentrations in air, the duration of exposure and the percental of individuals that may experience a specific toxicological endpoint, most often life-threatening effects [3, 4].

In this report, we have derived regression coefficients from AEGL-3 values and for comparison, we present the regression coefficients for lethality probit derived by RIVM (Netherlands' National Institute of Public Health and the Environment) [4]. Similarly, to AEGL, the RIVM procedure is based on a rigorous scientific review processes. The probit regression coefficients from RIVM are subject to recurrent review and revision based on new data and interpretation. To date (Nov 2018) the RIVM constants described here are interim or under re-evaluation by RIVM.

In this report we use the generally accepted table for probits (Pr), i.e. standard normal deviate +5 where 50% injured corresponds to Pr=5.00 [3] in comparison to previous

[1] Acute Exposure Guideline Levels (AEGLs), derived by the AEGL-committee at the U.S. National Research Council.

[2] Dangerous Toxic Load (DTL) for Specified Level of Toxicity (SLOT) and Significant Likelihood of Death (SLOD), derived by Health and Safety executive, UK

[3] Emergency Response Planning Guidelines (ERPG), developed by Emergency Response Planning committee of the American Industrial Hygiene Association

[4] https://rvs.rivm.nl/normen/rampen-en-incidenten/interventiewaarden Intervention Values for Dangerous Substances, developed by the Dutch Ministry of Housing, Spatial Planning and Environment. Life threatening values (LBW).

[5] Valeurs Seuils de Toxicité Aiguë Françaises (VSTAF): Threshold of Lethal Effects (SEL) and Threshold of Irreversible Effects (SEI), values provided at INERIS web-page https://substances.ineris.fr/fr/page/23#tabvst.

reports [5-8] using the standard normal deviate where 50% injured corresponded to Pr=0.00.

## Modelling levels of chemicals in air at different exposure scenarios

Information of chemical properties, their storage and transport are important to consider when performing health risk calculations. Chemicals that are volatile liquids at normal pressure and temperature can generate toxic clouds if released. The releases of toxic chemicals into the atmosphere may be due to an accidents or an antagonistic action. In both instances, the source can be of different characters and thereby have profoundly different properties. One example is industrial chemicals that are gaseous at normal pressure and temperature, while during transportation, they are kept in a condensed state using pressurized containers. A leakage from such pressurized container may cause drastic release into the surroundings.

Detailed understanding of an event is desired for different purposes for example 1) in the planning phase of a situation including a risk of a release, 2) during an ongoing event to provide intelligence on the region to cordon off or 3) in the aftermath of an event to investigate the exposure already experienced by a population to estimate the resulting health burden. The complete scenario is typically modelled, simulated and analysed to obtain the required information. The source term depends on the type of event but also the physical properties of the chemical. The atmospheric transport from the source is typically handled by numerical simulation, which provides a time dependent concentration field. A population exposed to this concentration field will experience a non-constant exposure. Traditionally, tables are available that present guidelines of exposure periods until different levels of injuries are acquired. However, these tables are based on constant concentrations, which is never the case in an actual situation. Probit functions are utilised to address this shortcoming since they are able to handle time-dependent concentration fields.

## Selection of toxic industrial chemicals

In this report we focus on toxic industrial chemicals that are present in smoke, and are irritant gases and/or are high production volume chemicals (HPV) world-wide[6] (table 1). We have included the chemicals studied from previous reports from FOI [5-8] with the addition of more chemicals that may be present in smoke emitted from fire.

In smoke emitted from fire, there are many potentially harmful products from the thermal degradation of materials. The mixture of gases emitted depends on the chemical composition of the burning material (composite material, cell plastic foam and additives such as plasticizers, flame-retardants, and UV-filters). In addition, the conditions during thermal degradation such as temperature and oxygen availability will affect the composition of the gases emitted. Two important gases that may be present in smoke from fires are carbon monoxide (CO) and hydrogen cyanide (HCN). Both of these are common causes of death following inhalation of smoke from fires [9-10].

All industrial chemicals chosen in our previous reports can be detected in smoke emitted from fire and/or combustion from petrol engines [11-13], although not produced during all conditions. Since fires are common and there is a risk of exposure, we have included four additional chemicals that can be found in smoke [11]. See selected industrial chemicals in table 1.

[6] OECD Existing Chemicals Database: https://hpvchemicals.oecd.org/UI/Search.aspx, visited 2017-11-20

**Table 1**. Industrial chemicals included in this report

| Irritant gas and HPV (OECD) | | Irritant gas | HPV** (OECD) |
|---|---|---|---|
| Acrolein* | Hydrogen chloride | Nitrogen dioxide | Acrylonitrile |
| Ammonia | Hydrogen fluoride | | Carbon monoxide* |
| Bromine | Hydrogen sulphide | | Ethylene oxide |
| Chlorine | Methyl isocyanate | | Hydrogen cyanide |
| Formaldehyde* | Phosgene | | |
| Hydrogen bromide* | Sulphur dioxide | | |

* Chemicals added in this report compared to previous reports from FOI/ (former FOA) [5-8].

** HPV: High production volume chemicals, according to OECD's (Organisation for Economic Co-operation and Development) Existing Chemicals Database: https://hpvchemicals.oecd.org/UI/Search.aspx, visited 2017-11-20

## Selection of chemical warfare agents

Chemical weapons are defined by OPCW as chemicals used to cause intentional death or harm through their toxic properties. The production, storage and use of nerve agents and sulphur mustard are banned by the Chemical Weapons Convention of 1993. Table 2 shows the chemical warfare agents selected for this report including certain industrial chemicals that are prohibited for use as chemical warfare agents.

**Table 2.** Chemical warfare agents included in this report

| | | |
|---|---|---|
| Chlorine* | Sulphur Mustard | Soman |
| Phosgene* | Sarin | VX |

* These chemicals are also listed as industrial chemicals in this report.

# Methods

## Time scaling

One of the challenges with AERV's is that data often are available for only a few exposure durations. To derive values for other exposure durations there is a need to perform time scaling. Haber's Law [14] was established for time scaling, where the toxic load (k) following a chemical exposure is linearly related to the concentration (C) multiplied by the duration of the exposure (t)

$$k = C \times t \qquad \text{(equation 1)}$$

Accordingly, a short exposure to a high concentration of a chemical in air and a long exposure to a low concentration in air of the same chemical are both expected to produce a similar degree of symptoms if both have the same value of k. However, not all gases apply to Haber´s law, i.e. a high concentration exposure for a short time may be lethal whereas a low concentration over a long exposure period may result in mild, transient effects. In addition, Haber´s law does not take into consideration the transformation or metabolism of a substance by an organism. Hence, a more extended equation has been developed to determine the toxic load [14]

$$k = C^n \times t \qquad \text{(equation 2)}$$

where the factor n is the toxic load exponent and describes the body's tolerance against the substance. According to a study from ten Berge *et al*., the n value can vary between 0.8 - 3.5 [14]. For substances that apply to Haber´s law, n is equal to 1 [14].

## Dose response modelling and toxicological endpoints

Dose response modelling provides quantitative information on the relationship between a chemical exposure and a predefined toxicological response. In this report we use data from AEGL-3. The exposure levels in AEGL-3 are based on data from animals, often time-scaled as equation 2, and always scaled to human conditions using assessment (safety) factors. The toxicological response rate used in AEGL-3 evaluation varies, but mostly a 1% or 5% response rate is applied with lethality as the response, i.e. at the AEGL-3 level a certain percentage (1% or 5%) of the exposed individuals may be lethality injured.

## Probit analysis

Probit functions (equation 3) describe the relationship between the concentration of a substance (C) and the duration of exposure (t) according to toxic load (equation 2) and the part of the exposed population (response rate) that demonstrates a certain effect.

Based on results from animal studies where an actual toxic effect takes place at known exposure durations and concentrations, the regression coefficients α and β are calculated (equation 3). The probit value (Pr) can be defined as the standard normal deviate + 5 [3; 15-16] where for instance a 5% response rate corresponds to a probit (Pr) of 3.36.

$$Pr = \alpha + \beta \times \ln (C^n \times t) \qquad \text{(equation 3)}$$

The equation 3 is sometimes written as $Pr=\alpha + (\beta_1 \times \ln(C)) + (\beta_2 \times \ln (t))$ where β in equation 3 is $\beta_2$ and $n= \beta_1/\beta_2$.

In this report we aimed to calculate the regression coefficients α and β. To calculate the β we used the method of RIVM where the β value is set to 2/n [4]. We used the n-value (toxic load exponent) presented in the AEGL-document for the specific chemical, if not specified otherwise.

When β was derived, the regression coefficient α was calculated for each chemical by using the equation 3. This was done by taking the average of the calculated α-values for each exposure duration (t) and the corresponding AEGL-3 value (C), including the regression coefficient of β, the n value from AEGL-3 and the probit (Pr) that matched the response rate in AEGL-3.

Our calculated regression coefficients were validated by comparing the original air concentrations in AEGL-3 with our calculated concentrations in air at the same response rate for each exposure duration. This was done by using α, β and n in the probit function at the response rate (Pr) used by AEGL. We also compared the derived concentrations in air using our calculated regression coefficients and those of RIVM at 5% response rate (Pr=3.36).

In previous reports, FOI/(former FOA) has used the standard normal deviate as the probit (as described in reference [8]) where the probit 0 corresponded to 50% response rate and -2.33 corresponded to 1% response rate. However, to avoid negative probits most publications add +5 to the standard normal deviate i.e. the probit (Pr) is 5 at 50% response rate and 2.67 at 1% response rate. In this report, we use the standard normal deviate + 5.

By doing this the α-value also changes correspondingly (+5) in comparison to previous FOI/(former FOA) reports.

# Results

## Regression coefficients and the toxic load exponent (n)

Based on the AERVs from AEGL-3, the regression coefficients α and β were calculated for the probit function (table 3). Table 3 also lists the toxic load exponent (n) from AEGL-3 ($n_A$).

According to AEGL, the toxic load exponent (n) is non-linear for carbon monoxide, sulphur dioxide and sulphur mustard. The n for carbon monoxide was calculated with linear regression analysis of a log(t)-log(C) curve (see reference [2], in appendix G) using animal data given by AEGL-3 [37]. For sulphur dioxide, n was calculated as an average of the n given for the exposure periods 30 min, 1, 4 and 8 h [49]. For sulphur mustard the n-value was the n given in the AEGL-3 document for 100% response of mild ocular irritation ([52], in appendix B).

There are some exceptions when using these regression coefficients. When calculating the probit equation for hydrogen chloride and hydrogen fluoride at exposure periods of 240 min or more, the exposure period of 240 min should be entered into the equations since the AEGL-3 value for 240 min is the same as for AEGL-3 at 480 min. Also, when calculating the probit equation for sulphur dioxide at exposure periods of 60 min or less, the exposure period of 60 min should be entered into the equation since the AEGL-3 value at 30 min is the same as for AEGL-3 at 60 min.

We also present in table 3 the corresponding toxic load exponent from RIVM ($n_R$) and the regression coefficients α and β derived by RIVM [17-52].

**Table 3.** Regression coefficients (α and β) for the probit function with risk of life-threatening injuries as endpoint. Data shown are the calculated α and β based on data from AEGL-documents and those derived and published by RIVM. The table also shows the exponent n as determined by AEGL and RIVM respectively. The regression coefficients are valid for concentration in air using mg/m$^3$ as the unit and exposure period using min as the unit.

| **Chemical** | **N** | | **β (2/n)** | | **α** | | **References** | | **Status Nov 29, 2018** |
|---|---|---|---|---|---|---|---|---|---|
| | from RIVM ($n_R$) | from AEGL-3 ($n_A$) | from RIVM ($\beta_R$) | via AEGL-3 ($\beta_A$), Note[5] | from RIVM ($\alpha_R$) | via AEGL-3 ($\alpha_A$), Note[6] | RIVM | AEGL | RIVM, Note[9] |
| Acrolein | 1.08 | 1.2 | 1.85 | 1.7 | -9.79 | -6.57 | [7] | [33] | Interim |
| Acrylonitrile | 1.19 | 1.1 | 1.69 | 1.8 | -17.3 | -12.47 | [18] | [34] | Interim |
| Ammonia | 2.02 | 2 | 0.99 | 1 | -16.49 | -14.73 | [19] | [35] | Interim |
| Bromine | 1.28 | 2.2 | 1.57 | 0.9 | -12.19 | -9.07 | [20] | [36] | Interim |
| Carbon monoxide | 1.81 | 1.81 Note1 | 1.11 | 1.1 | -15.91 | -13.93 | [21] | [37] | Interim |
| Chlorine | 1.04 | 2 | 1.93 | 1 | -13.66 | -9.55 | [22] | [38] | Interim |
| Ethylene oxide | 2 | 1.2 | 1 | 1.7 | -17.50 | -15.92 | [23] | [39] | Interim |
| Formaldehyde | 3.70 | 3 | 0.54 | 0.7 | -8.21 | -8.63 | [24] | [40] | Interim |
| Hydrogen bromide | ND | 1 | ND | 2 | ND | -16.83 | - | [41] | - |
| Hydrogen chloride | 1.37 | 1 Note 2 | 1.46 | 2 | -17.09 | -15.62 Note 7 | [25] | [42] | Interim |
| Hydrogen cyanide | 1.71 | 2.6 | 1.17 | 0.8 | -9.38 | -6.13 | [26] | [43] | Interim |
| Hydrogen fluoride | 1.09 | 2 Note 2 | 1.83 | 1 | -13.20 | -7.90 Note 7 | [27] | [44] | Interim |
| Hydrogen sulphide | 6.52 | 4.4 | 0.31 | 0.5 | -7.86 | -7.73 | [28] | [45] | Interim |

| Chemical | n | | β (2/n) | | α | | References | | Status Nov 29, 2018 |
|---|---|---|---|---|---|---|---|---|---|
| | from RIVM ($n_R$) | from AEGL-3 ($n_A$) | from RIVM ($\beta_R$) | via AEGL-3 ($\beta_A$), Note[5] | from RIVM ($\alpha_R$) | via AEGL-3 ($\alpha_A$), Note[6] | RIVM | AEGL | RIVM, Note[9] |
| Methyl isocyanate | 1.01 | 1 | 1.98 | 2 | -10.30 | -4.03 | [29] | [46] | Proposed |
| Nitrogen dioxide | 3.99 | 3.5 | 0.50 | 0.6 | -7.76 | -6.96 | [30] | [47] | Interim* |
| Phosgene | 0.80 | 1 | 2.51 | 2 | -10.64 | -7.74 | [31] | [48] | Interim |
| Sulphur dioxide | 2 | 2 Note 3 | 1 | 1 | -12.60 | -9.53 Note 8 | [32] | [49] | Interim |
| Sarin (GB) | ND | 2 | ND | 1 | ND | 2.55 | - | [50] | - |
| Soman (GD) | ND | 2 | ND | 1 | ND | 2.55 | - | [51] | - |
| Sulphur mustard | ND | 1.11 Note 4 | ND | 1.8 | ND | -5.85 | - | [52] | - |
| VX | ND | 2 | ND | 1 | ND | 7.70 | - | [53] | - |

Note[1] to $n_A$: According to AEGL, n is non-linear. The n-value was calculated with linear regression analysis of a logt- logC curve of animal data given by AEGL (for method see reference [2], appendix G).

Note[2]: Use the exposure period of 240 min in the probit equation when calculating for exposure periods >240min.

Note[3] To $n_A$: According to AEGL n is non-linear. The n-value was calculated as an average of n for the exposure periods 30 min, 1, 4 and 8 h. Use the exposure period of 60 min in the probit equation when calculating for exposure periods <60 min.

Note[4] To $n_A$: According to AEGL n is non-linear. The n-value used here was the n from the AEGL-3 document ([52] appendix B) for 100% response of mild ocular irritation.

Note[5]: β was calculated with RIVMs equation 2/n using an n-value (or an average value) as stated in the AEGL-document.

Note[6]: $\alpha=Pr-\beta*\ln(C^n*t)$. Individual α-values were calculated at the exposure periods 30 min, 1, 4 and 8 h using the corresponding AEGL-3 value for each chemical. The presented α-values ($\alpha_A$) represent an average value.

Note[7]: The $\alpha_A$ was calculated as an average of 30 min, 1 and 4 h. AEGL uses the 4 h value also at 8 h.

Note[8]: The $\alpha_A$ was calculated as an average of 1, 4 and 8 h. AEGL uses the 1 h value also at 30 min.

Note[9]: Published on: https://www.rivm.nl/en/Topics/P/Probit_functions/Probit_function_status_overview. Visited 2018-11-29

*www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Uitgaven/Milieu_Leefomgeving/Probits/Technical_support_documents/Stikstofdioxide/Download/20180504_nitrogen_dioxide_interim. Visited 2018-11-29.

## Comparison of AEGL-3 values with those calculated by FOI

In table 4, we have compared the listed AEGL-3 concentrations in air for two exposure periods with the calculated concentrations in air using the regression coefficients in the probit based on AEGL-3, presented in table 3. In order to compare the values, we used an equivalent response rate of lethality as presented in the AEGL-3 documents in the probit functions. However, in some cases the AEGL-3 documents do not use death as an endpoint (acrolein, chlorine, formaldehyde, hydrogen sulphide and phosgene). The endpoint of non-lethality for these chemicals is highly dependent on the dose selection and may potentially over-estimate the risk of the chemical.

Other chemicals that have used other endpoints than death is carbon monoxide and methyl isocyanate. The endpoint of carbon monoxide is based on human studies and refer to the concentration of carbon monoxide that binds to haemoglobin causing non-lethal effects (CoHb 40%). The endpoint of methyl isocyanate is based on the highest dose that does not cause death in mouse pups (the No Observed Effect Level).

**Table 4.** AEGL-3 values at exposure periods 30 min and 240 min in comparison to calculated values at the corresponding exposure period using the same response rate as stated in the AEGL documents. 1% response rate is equivalent to Pr=2.67 and 5% is equivalent to Pr=3.36.

| **Chemicals** | **Response rate (%) AEGL-3**<br>See Note[1] | **AEGL-3**<br>mg/m$^3$<br>30 min | **Calculated values** using $n_A$, $\alpha_A$ and $\beta_A$ from table 3. Same response rate as AEGL-3<br>mg/m$^3$<br>30 min | **AEGL-3**<br>mg/m$^3$<br>240 min | **Calculated values** using $n_A$, $\alpha_A$ and $\beta_A$ from table 3. Same response rate as AEGL-3<br>mg/m$^3$<br>240 min |
|---|---|---|---|---|---|
| Acrolein | Highest non-lethal* | 5.7 | 6.0 | 1.1 | 1.1 |
| Acrylonitrile | 5% | 110 | 124 | 21 | 19 |
| Ammonia | 1% | 1119 | 1097 | 385 | 388 |
| Bromine | 1% | 78 | 75 | 29 | 29 |
| Carbon monoxide | CoHb 40% nonlethal to humans* | 690 | 615 | 170 | 195 |
| Chlorine | Highest non-lethal* | 81 | 82 | 29 | 29 |
| Ethylene oxide | 1% | 648 | 641 | 113 | 113 |
| Formaldehyde | Highest non-lethal* | 86 | 91 | 43 | 46 |
| Hydrogen bromide | 5% | 830 | 807 | 100 | 101 |
| Hydrogen chloride | 1/3 of $LD_{50}$ 1h* | 313 | 312 | 39 | 39 |
| Hydrogen cyanide | 1% | 23 | 22 | 9.7 | 9.9 |
| Hydrogen fluoride | 5% | 51 | 51 | 18 | 18 |
| Hydrogen sulphide | Highest non-lethal, 1h* | 85 | 84 | 52 | 52 |
| Methyl isocyanate | NOEL pup survival* | 0.95 | 0.95 | 0.12 | 0.12 |
| Nitrogen dioxide | Irritation, no death* | 47 | 47 | 26 | 26 |
| Phosgene | Highest non-lethal* | 6.2 | 6.1 | 0.82 | 0.76 |
| Sulphur dioxide | 5% | 78 | 81<br>Note[2] | 49 | 41 |
| Sarin (GB) | 1% | 0.19 | 0.19 | 0.07 | 0.07 |
| Soman (GD) | 1% | 0.19 | 0.19 | 0.07 | 0.07 |
| Sulphur mustard | 1/2 of $LC_{50}$* | 2.7 | 3.31 | 0.53 | 0.51 |
| VX | 1% | 0.015 | 0.015 | 0.0052 | 0.0052 |

Note[1]: Animal studies if not stated otherwise.

Note[2]: Since AEGL-3 for sulphur dioxide is the same for both 30 min and 1 h, the calculated value represents the 1 h value.

* AEGL has not stated a value for the response rate and was here estimated to 1%.

For most chemicals, there is a good fit between the AEGL-3 values and the calculated values based on probit functions derived via AEGL-3. In figure 1, three examples are presented (A) a good fit of the curve, (B) an intermediate fit and (C) a poor fit of the curve. Chemicals with an intermediate fit had one or more exposure periods with >5% difference from corresponding AEGL-3 value (acrylonitrile and phosgene). Chemicals with a poor fit had one or more exposure periods with ≥15% difference from corresponding AEGL-3 value (carbon monoxide, formaldehyde, sulphur dioxide and sulphur mustard). The largest percental disparity was sulphur mustard at short exposure durations, e.g. 23% at 30 min and 16% at 60 min.

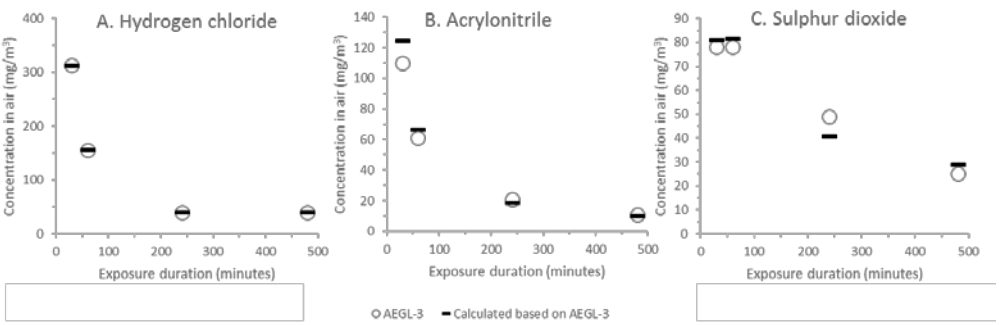


**Figure 1.** AEGL-3 concentrations in air compared to calculated values derived using regression coefficients and exponent (n) from our probit analysis based on AEGL-3 values. The response rate for each chemical as stated in the corresponding AEGL document.

## Comparison of concentrations in air at 5% response rate

The probit function can be used to assess probability of human survivability at various levels of concentration in air up to eight hours of exposure. However, depending on the toxicity data used, the modelling and decisions of assessment (safety) factors will affect the regression coefficients. The results in table 5, show the differences between RIVM and FOIs calculated concentrations in air based on AEGL-3 for two exposure periods (30 min and 240 min) at a 5% response rate (Pr=3.36). In most cases, the calculated concentration derived via the probit functions from RIVM are higher than those derived via the probit functions based on AEGL-3, i.e. AEGL-3 estimates that life-threatening effect may occur at lower levels of exposure.

The average ratio of the RIVM-derived values divided by the value derived via AEGL-3 probit was calculated for each chemical. The average ratios were categorised as relatively close correlation (0.99-1.34), intermediate correlation (1.4-2.6) and low level of correlation (3.3-24). In figure 2, three examples are presented. Chemicals with a relatively close correlation were bromine, chlorine, formaldehyde, and phosgene. The intermediate correlated chemicals were hydrogen cyanide, hydrogen fluoride, hydrogen sulphide, nitrogen dioxide, and ammonia.

This shows that an estimate of the concentration in air at a certain response rate and exposure period may differ, most likely due to the fact that they are based on different studies, different interpretation of toxicity data, and differences in the use of assessment factors to extrapolate / translate results from animals to humans.

**Table 5**. Comparison of concentrations in air (C) for a 5% (Pr=3.36) response rate at the exposure periods 30 min and 240 min calculated with regression coefficients and exponent (n) from RIVMs probit analysis and those derived via AEGL-3.

| **Chemicals** | **Calculated concentration in air for 5% response rate using** | | | |
|---|---|---|---|---|
| | **$n_A$, $\alpha_A$ and $\beta_A$ in table 3 (FOI, based on AEGL-3)** mg/m$^3$, 30 min ($C_A$) | **$n_R$, $\alpha_R$ and $\beta_R$ in table 3 (RIVM),** Note[2] mg/m$^3$, 30 min ($C_R$) | **$n_A$, $\alpha_A$ and $\beta_A$ in table 3 (FOI, based on AEGL-3)** mg/m$^3$, 240 min ($C_A$) | **$n_R$, $\alpha_R$ and $\beta_R$ in table 3 (RIVM),** Note[2] mg/m$^3$, 240 min ($C_R$) |
| Acrolein | 8 | 31 | 1 | 5 |
| Acrylonitrile | 124 | 1660 | 19 | 289 |
| Ammonia | 1549 | 3817 | 548 | 1363 |
| Bromine | 107 | 162 | 41 | 32 |
| Carbon monoxide | 868 | 2224 | 275 | 705 |
| Chlorine | 116 | 187 | 41 | 25 |
| Ethylene oxide | 905 | 6182 | 160 | 2186 |
| Formaldehyde | 129 | 130 | 64 | 74 |
| Hydrogen chloride | 440 | 2313 | 55 | 507 |
| Hydrogen cyanide | 31 | 80 | 14 | 24 |
| Hydrogen fluoride | 51 | 178 | 18 | 26 |
| Hydrogen sulphide | 118 | 154 | 74 | 112 |
| Methyl isocyanate | 1.3 | 32 | 0.2 | 4 |
| Nitrogen dioxide | 66 | 112 | 36 | 67 |
| Phosgene | 9 | 16 | 1 | 1 |
| Sulphur dioxide | 81 Note[1] | 533 | 41 | 189 |

Note[1] since AEGL-3 for sulphur dioxide is the same for both exposure periods 30 min and 1 h, the calculated value represents the 1 h value.

Note[2] RIVM has not published regression coefficients and n-values for hydrogen bromide, nerve agents and sulphur mustard, hence these chemicals were excluded from this table.

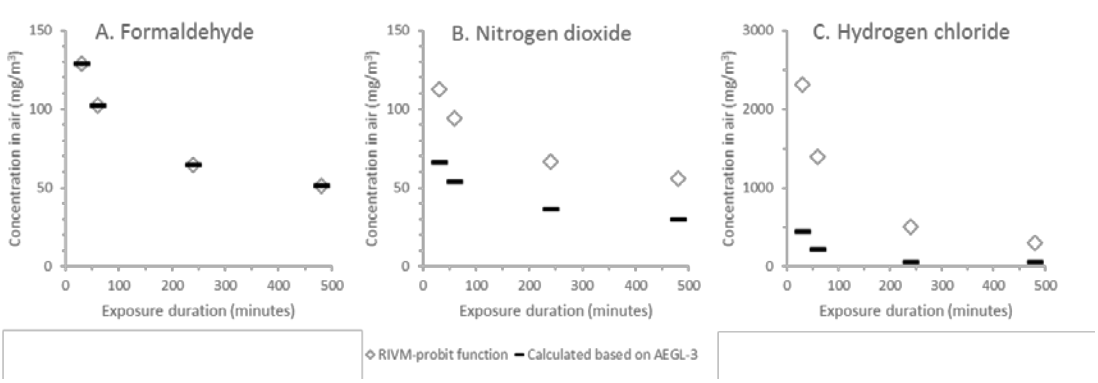


**Figure 2.** Comparison of the chemical concentrations in air derived via RIVM (diamond) with the chemical concentrations in air derived from our calculated probit analysis based on AEGL-3 values (black line). The response rate was 5% (Pr=3.36).

## Conclusion

The probit function can be used to interpret acute health risks in a scenario or after an actual release of a chemical to air illustrated by dispersion models developed at FOI. This report provides values of the regression coefficients alpha (α) and beta (β) for the probit function based on AEGL-3 values with use of the methodology from RIVM (The Netherlands) concerning the calculation of the β-values. The toxic industrial chemicals included here can be detected in smoke, and are irritant gases and/or are high production volume chemicals world-wide. We have also included chemical warfare agents.

In general, there is a high degree of similarity between AEGL-3 values (chemical concentrations in air at defined time-points) and those derived from regression coefficients calculated in this report. There are, however, differences between the RIVM and FOIs calculated chemical concentrations in air based on AEGL-3. This can be explained by the use of different scientific studies, differences in the interpretation of toxicity data, and the use of different assessment (safety) factors to extrapolate / translate results from animal to human, and if sensitive individuals are considered or not. We have not analysed the contribution of these factors. We suggest that the probit functions derived by RIVM are used to calculate response rates of the general population where there is a risk of lethal exposure after a chemical emission. Furthermore, probit functions based on AEGL-3 are recommended by us to be used for chemicals where probit functions have not been published by RIVM. Concerning chemicals included in this report, RIVM has not published data for chemical warfare agents and hydrogen bromide.

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