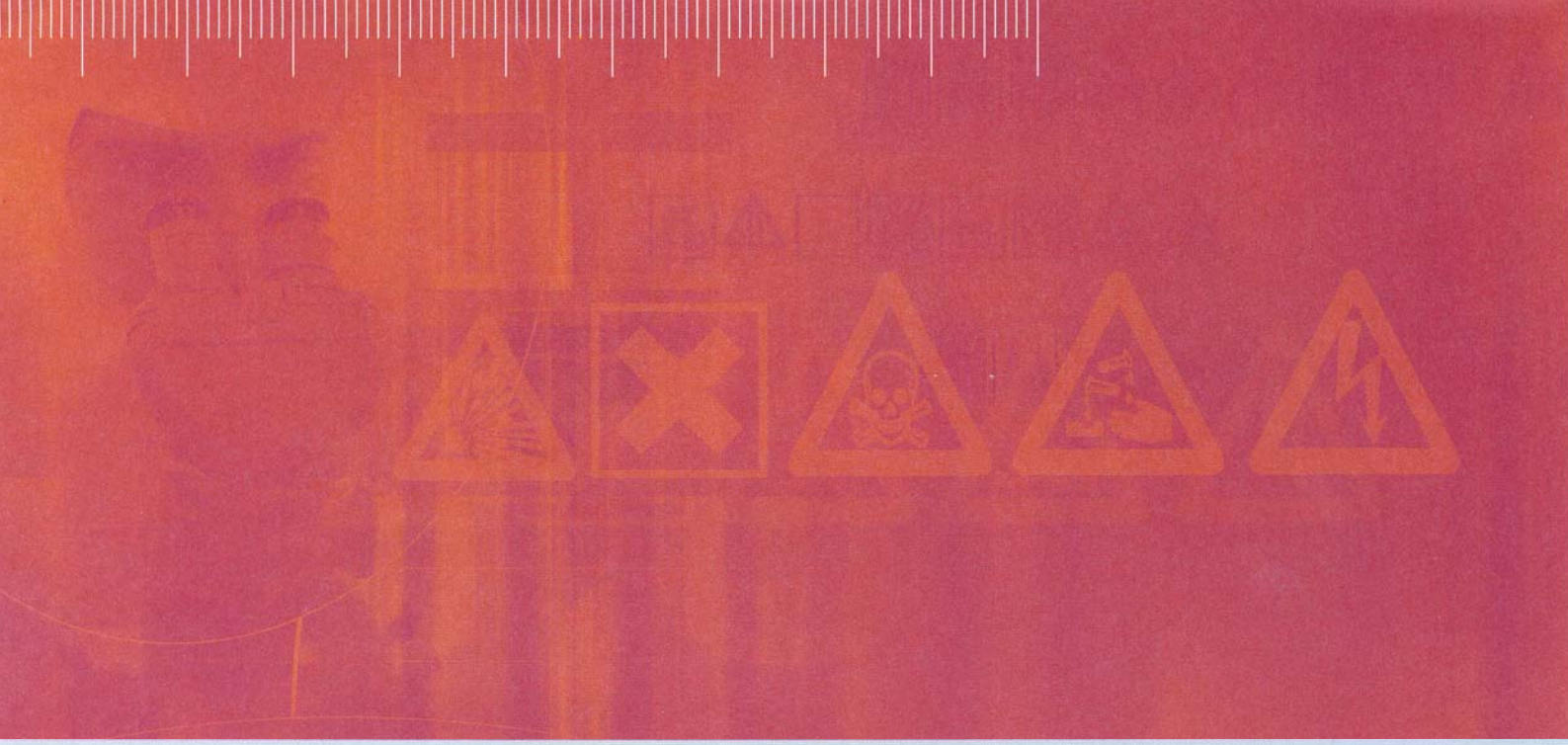

STUDY REPORT 24/07/2009

No.DRC-09-103128-07577A-

# Technical Guidance document for selecting acute toxicity threshold values in the absence of official French values.

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controlling risks for sustainable development

# Technical guidance for selecting acute toxicity threshold values in the absence of official French values

Chronic Risk Division
*Expertise and Evaluations in Toxicology Unit*

Client: Ministry of Ecology, Energy, Sustainable Development and National Planning

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# 1. GLOSSARY

AEGL: Acute Exposure Guideline Level

AETL: Acute Exposure Thresholds Level

AGW: Alarmeringsgrenswaarde – Alarming threshold

AIHA: American Industrial Hygienist Association

DIG: Dutch Intervention Guidelines

DTL: Dangerous Toxic Load

ECETOC: European Center for Ecotoxicology and Toxicology of Chemicals

EDD: *Etude De Dangers* - Hazard Study

EEI : Emergency Exposure Indices

ERPG : Emergency Response Planning Guideline

IC: *Installation Classée* - Classified Installation

IDLH: Immediately Dangerous Life Hazard

LBW: Levensbedreigende waarde – Life threatening value

LDSA: Level of Distinct Sensory Awareness

LOAEL: Low Observed Adverse Effect Level

MEDAD: *Ministère de l'Ecologie, du Développement et de l'Aménagement Durables* - Ministry of Ecology, Sustainable Development and Planning

MEEDDAT : Ministère de l'Ecologie, de l'Energie, du Développement Durable et de l'Aménagement Durable - Ministry of Ecology, Energy, Sustainable Development and Planning

NOAEL : No Observed Adverse Effect Level

POD: Point Of Departure

PPRT: *Plans de Prévention des Risques Technologiques* - Technological Risk Prevention Plans -

SDIS: *Service Départemental d'Incendie et de Secours* - Departmental Fire and Rescue Service -

SELS: *Seuil des Effets Létaux Significatifs* - Significant Lethal Effects threshold

SEI: *Seuil des Effets Irréversibles* - Irreversible Effects threshold

SER: *Seuil des Effets Réversibles* - Reversible Effects threshold

SLOD: Significant Likelihood of Death

SLOT: Specified Level of Toxicity

SPEL: *Seuil des Premiers Effets Létaux* - First Lethal Effects threshold

SP: *Seuil de Perception* - Perception Threshold

TEEL : Temporary Emergency Exposure Level

US-EPA: US Environment Protection Agency

VRW: Voorlichtingsrichtwaarde – Communication guideline value

VLE: *Valeur Limite d'Exposition*, Exposure Limit Value

VME: *Valeur Limite de Moyenne d'Exposition*, Average Exposure Limit Value

VSTAF : *Valeurs Seuils de Toxicité Aiguë Françaises*, French Acute Toxicity Threshold Values

# 2. INTRODUCTION

The French acute toxicity threshold values (VSTAF) are reference values for classified installations (IC) in France. From the scenarii of dangerous phenomena established by the hazard assessment studies (EDD), they are used to determine the zones of lethal, irreversible and reversible effects relative to the location of plants storing, producing or using toxic substances.

A set of VSTAFs were initially published in 1998 by the Ministry responsible for the environment in the document entitled “Fiches techniques - Courbes de toxicité par inhalation” (“Technical documents – Inhalation toxicity curves”).

In 1999, the “Industrial Environment Service” (SEI), within the Pollution and Risk Prevention Direction (DPPR) of the Ministry of Ecology, Energy, Sustainable Development and National Planning (MEEDDAT), asked the Institut National de l’Environnement industriel et des Risques (INERIS, National Institute for the Industrial Environment and Risks) to revise the 24 VSTAFs of the 1998 document and to develop thresholds for new substances. INERIS therefore developed a methodology[1] which was published on August 20, 2003 and revised in December 2007 with the concern of preserving the traceability of the scientific and technical data which were used for determining the updated VSTAFs. The methodology and reports may be accessed on the INERIS website (www.ineris.fr).

A problem arises when there are no VSTAFs. In that case, it is the responsibility of the company conducting the hazard assessment study to propose values for lethal, irreversible and reversible effects. To do that, a company has two possibilities:

- ✓ either to produce a summary of the acute toxicity studies in animals and/or humans for the relevant substance, public data or specific to the company, and to determine values for lethal, irreversible and reversible effects according to the French methodology in force;
- ✓ or to use existing values at the European or international level.

The present guidance document is intended for companies or any other operator or administrations that wish to have a method for selecting acute toxicity thresholds for lethal, irreversible and reversible effects based on the numerous values existing at the European and international levels.

Concerning the perception threshold, there is no consensus at the European or international levels at this time, and it has therefore been decided not to treat this threshold in this guidance document.

A first section presents a table summarizing all of the acute toxicity thresholds by inhalation available in the literature. For each of them, the exact definition, the issuing body and the purpose for which these values were determined, and lastly the means for accessing the information, are given. For some of them, it will be possible to obtain the complete evaluation reports, which are a useful reference source of toxicity data in humans and animals.

[1] Institut national de l’environnement industriel et des risques (INERIS). Methodology for determining French acute toxicity Thresholds of lethal effects, irreversible effects and reversible effects. Verneuil-en-Halatte: INERIS, 2007; 24 p.

In a second part, two methods for selecting these values are proposed, which differ in purpose: a method for land use planning (LUP) and another for emergency management. In the method proposed for LUP, depending on the toxicology skills of the assessor and available data, four tiered levels are available.

The thresholds obtained using these methods, in particular level four, are provided for informational purposes, and it is always necessary first to try to determine thresholds according to the French methodology.

# 3. EXISTING ACUTE TOXICITY THRESHOLD VALUES

At the USA and European levels, a number of acute toxicity threshold values are available, among which it may be difficult to make a reasoned selection. Indeed, each type of values has its own definition and was developed for specific purposes, mostly for emergency situations, in order to protect the general population and take the appropriate risk management measures. Their diversity is rather related to their uses and the usage for which these acute toxicity values are intended than to real divergences of definitions. Another important factor explaining these differences in numerical values is the targeted population (general population, workers, susceptible sub-populations) and the safety factors which may or not be taken into account in order to cover the specificities of the target population.

In order to enlighten the reader, the following summary table gives a concise description of each type of values and to present the advantages and major drawbacks thereof.

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| AEGL[2] (*US-EPA*) | **AEGL-1:** the airborne concentration (ppm) of a substance above which it is predicted that the general population, including susceptible 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.<br><br>**AEGL-2:** the airborne concentration (ppm) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.<br><br>**AEGL-3:** the airborne concentration (ppm) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death. | 10, 30 min<br>1, 4 and 8 h |
| | **Target population**: general population including susceptible individuals<br><br>**Internet Address**: http://www.epa.gov/oppt/aegl/pubs/chemlist.htm<br><br>**Origin** : AEGL NAC (National Advisory Committee) US<br><br>**Availability of a scientific report**: yes, for substances finalized and published in the Federal Register<br><br>**Advantage:** gives thresholds for lethal, irreversible and reversible effects for the general population for 5 exposure times, availability of a methodology for thresholds determination, and of scientific reports<br><br>**Drawback**: the thresholds are defined above a critical concentration (~concentration without any effect) for emergency situations; sometimes using very important protection factors to take susceptible populations into account (protective compared to the French methodology).<br><br>Level 3 (lethal effects) corresponds to a threshold without obvious lethal effects | |

[2] ***AEGL**: Acute Exposure Guideline Levels*

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| ERPG[3] (*AIHA*) | **ERPG-1:** the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 hour without experiencing more than mild, transient adverse health effects or without perceiving a clearly defined objectionable odour.<br><br>**ERPG-2:** the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.<br><br>**ERPG-3:** the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects. | 1 h |
| | **Target population**: not clearly defined, workers in priority<br><br>**Internet Address**: http://www.aiha.org/content/insideaiha/volunteer+groups/erpcomm.htm<br><br>**Origin**: American Industrial Hygiene Association (AIHA)<br><br>**Availability of a scientific report**: no<br><br>**Advantage:** thresholds for lethal, irreversible and reversible effects corresponding to a real critical effect. Developed for emergency situations<br><br>**Drawback**: the thresholds are determined for a single exposure time and scientific reports are not available. | |

[3] ***ERPG****: Emergency Response Planning Guidelines*

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| TEEL[4] (*US-DOE*) | **TEEL-0**: the threshold concentration below which most people will experience no appreciable risk of health effects<br>**TEEL-1**: the maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odour.<br>**TEEL-2**: the maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing or developing irreversible or other serious health effects or symptoms that could impair their abilities to take protective action.<br>**TEEL-3**: the maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing or developing life-threatening health effects. | 15 min (for concentration-dependant chemicals) or 60 min (for dose-dependant chemicals) |
| | **Target population**: individuals present on US Energy Department sites, extension to transport of materials<br><br>**Internet Address**: http://orise.orau.gov/emi/scapa/teels.htm<br><br>**Origin**: US Department of Energy, developed when ERPGs are not available for emergency situations<br><br>**Availability of a scientific report**: no<br><br>**Advantage:** many values are available<br><br>**Drawback**: a single exposure time, development from professional exposure limit values or repeated use of the IDLH (cf following pages) or ERPGs. No scientific report. | |

[4] ***TEEL****: Temporary Emergency Exposure Levels (www.eh.doe.gov/chem_safety//teel.html)*

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| EEI[5] (*ECETOC*) | **EEI-1:** the maximum airborne concentration below which the exposed population is not likely to suffer discomfort.<br><br>**EEI-2:** the maximum airborne concentration below which the exposed population is not likely to suffer irritation.<br><br>**EEI-3:** the airborne concentration below which the exposed population is not likely to be incapacitated. | 15, 30 and 60 min |
| | **Target population**: general population including susceptible individuals and excluding the hyper-susceptible<br><br>**Internet Address**: www.ecetoc.org<br><br>**Origin**: ECETOC, European Center for Ecotoxicology and Toxicology of Chemicals<br><br>**Availability of a scientific report**: thresholds and reports not directly available<br><br>**Advantage:** takes susceptible populations but not hyper-susceptible populations into account with good representativity of general population within society<br><br>**Drawback**: few substances, no scientific report available | |

[5] ***EEI**: Emergency Exposure Indices*

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| IDLH[6] (*NIOSH*) | **IDLH (1987):** maximum airborne concentration up to which a person exposed for no more than 30 minutes could escape without risking irreversible health effects.<br><br>**IDLH (1994)**: an atmospheric concentration of any toxic, corrosive or asphyxiant substance that poses an immediate threat to life or would cause irreversible or delayed adverse health effects or would interfere with an individual's ability to escape from a dangerous atmosphere) | 30 min |
| | **Target population**: workers<br><br>**Internet Address**: http://www.cdc.gov/niosh/idlh/idlh-1.html<br><br>**Availability of a scientific report**: no, summary with reference for key studies and justification for the revision of values<br><br>**Advantage:** a fairly large set of values for irreversible effects<br><br>**Drawback**: workers which are most often pre-exposed to the substances, only one exposure time, scientific approach sometimes obscure and change in definition between 1987 and 1994.<br><br>Reminder: only the 1994 values should be taken into account. | |

[6] ***IDLH**: Immediately Dangerous to Life and Health*

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| VSTAF[7] (*MEEDDAT*) | **SPEL:** Thresholds of first lethal effects : the airborne concentration, for a given exposure duration, above which 1% mortality can be observed in the exposed population.<br><br>**SELS:** Thresholds of significant lethal effects: the airborne concentration, for a given exposure duration, above which 5% mortality can be observed in the exposed population .<br><br>**SEI**: Thresholds of irreversible effects : the airborne concentration, for a given exposure duration, above which irreversible effects may appear in the exposed population.<br><br>**SER**: Thresholds of reversible effects : the airborne concentration, for a given exposure duration, above which reversible effects may appear in the exposed population.<br><br>**SP**: Thresholds of sensory awareness : concentration, for a given exposure duration, that leads to a sensorial detection of the chemical substance by the exposed population (most often olfactory detection)) | 1, 10, 20, 30, 60, 120, 240 and 480 min |
| | **Target population**: general population excluding susceptible and hyper-susceptible individuals<br><br>**Internet Address**: www.ineris.fr/<br><br>**Origin**: MEEDDAT toxicological experts group, values with regulatory status<br><br>**Availability of a scientific report**: yes, as well as summary sheet<br><br>**Advantage:** takes death into account as a critical effect for lethal effects, good adequation with the requirements of land use planning regulation, exposure times from 1 to 480 minutes. Availability of a methodology for determining thresholds.<br><br>**Drawback**: limited number of substances, susceptible populations not taken into account, validity limit for exposure time of one minute. | |

[7] ***VSTAF****: Valeurs Seuils de Toxicité Aiguë Françaises* [French Acute Toxicity Threshold Values]

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| AETL[8] (*ACUTEX*) | **AETL-3a:** the airborne concentration at which it is predicted that after a specified exposure time a certain (i.e. 1,5 and 50%) percentage of the general population will die.<br><br>**AETL-3b**: maximum airborne concentration at which it is predicted the general population could be exposed up to a specified exposure time without experiencing life threatening health effects or death.<br><br>**AETL-2**: the maximum airborne concentration at which it is predicted the general population could be exposed up to a specified exposure time without experiencing or developing irreversible or other serious adverse health effects including symptoms that could lead to impairment to escape.<br><br>**AETL-1**: the maximum airborne concentration at which it is predicted the general population could be exposed up to a specified exposure time without experiencing more than mild and reversible adverse health effects.<br><br>**LDSA**: is the airborne concentration at which it is predicted that a proportion of the general population* could experience sensory stimuli (e.g. odour) that may lead to public complaints, concerns or even panic. | 10, 30, 60, 120, 240 and 480 min |
| | **Target population**: general population and additional factors for susceptible sub-populations<br><br>**Internet Address**: http://circa.europa.eu/Public/irc/jrc/Home/main<br><br>**Origin**: ACUTEX European research project (FP5)<br><br>**Availability of a scientific report**: no (not public).<br><br>**Advantage:** values developed to cover the needs for land use planning and emergency situations, makes it possible to take susceptible populations into account<br><br>**Drawback**: no scientific validation (peer review) of the whole of the values, nor official status of these values | |

[8] ***AETL**: Acute Exposure Threshold Levels*

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| DTL[9] (*UK-HSE*) | **SLOT**: the airborne concentration level at which almost everyone in the exposed area is likely to suffer severe distress, a substantial fraction of which will require medical attention, and some people will be seriously injured, requiring prolonged treatment. For highly susceptible people, the possibility exists that they will be killed.<br><br>**SLOD**: the airborne concentration level at which the mortality of 50% of an exposed population is predicted. | Independent of exposure time |
| | **Target population**: general population, including the hyper-susceptible individuals.<br><br>**Internet Address**: http://www.hse.gov.uk/hid/haztox.htm<br><br>**Origin**: UK Health and Safety Executive<br><br>**Availability of a scientific report**: no<br><br>**Advantage:** time-concentration pair, calculation is possible regardless of exposure time, developed for land use plannnig<br><br>**Drawback**: uses a mortality rate of 50% | |

[9] ***DTL****: Dangerous Toxic Load*

| Type of values | Definitions and comments | Exposure time |
|---|---|---|
| DIG[10] (*RIVM*) | **LBW**: the concentration of a substance above which death or a life threatening condition may develop within a few days after an exposure of one hour.<br><br>**AGW**: the concentration of a substance above which irreversible or other serious health impairment may occur as a result of acute toxic effects after an exposure of one hour.<br><br>**VRW**: the concentration of a substance at which with a high level of probability will be perceived by the majority of the exposed population as hindrance or above which minor, quickly reversible health effects may occur after an exposure of one hour. Often this is the concentration at which exposed people start to complain about the perceived exposure. | 60 min |
| | **Target population**: general population including susceptible populations (sex, age, pathology) but excluding the hyper-susceptible<br><br>**Internet Address**: http://www.rivm.nl/<br><br>**Origin**: RIVM<br><br>**Availability of a scientific report**: no<br><br>**Advantage:** -<br><br>**Drawback**: in Dutch language (no all documents translated into English), values not easily accessible | |

Table 1: summary of existing acute toxicity threshold values

Among all of the thresholds presented, it is appropriate, due to their scientific relevance and availability, to only use the following thresholds when making a selection in the absence of French values: AEGLs, ERPGs, IDLHs and TEELs.

The order in which these thresholds should be used is specified in chapter 4.

[10] ***DIG**: Dutch Intervention Guidelines*

# 4. METHODOLOGY FOR SELECTING THRESHOLD VALUES IN THE ABSENCE OF FRENCH VALUES

## 4.1 INTRODUCTION

VSTAFs are the regulatory reference thresholds for classified installations. In the absence of VSTAFs, the issue therefore arises of selecting the threshold values to be considered when performing hazard assessment (part 4.3), or even for emergency situations of the accidental type (part 4.4). Two methodologies are proposed for selecting the threshold values from the existing values at the international level depending on the relevant situation and toxicology skills needed for analyzing the data.

The only appropriate thresholds are the AEGLs, ERPGs, IDLHs and TEELs.

## 4.2 FIRST STEP: REVIEW

This step consists of consulting different Internet web sites in order to compile all of the available threshold values (AEGL, ERPG, IDLH and TEEL).

For each of the available values, with the exception of TEELs, and for each level of thresholds, one should identify, when available, the key study and the data used for determining the threshold values. The initial data required for determining the thresholds are the number of animals tested (total and per group), the exposure concentrations, the exposure time(s) and the related toxic effects.

For the TEELs, only $CL_{X\%}$ are available. The key study which was used for developing the values (lethal concentration, exposure time, exposed species) should be identified, but this information is rarely available. Thus, the quality and robustness of the source data used cannot be evaluated. This is why TEELs should only be used as a last resort and, in the case of land use planning, only as a basis for calculations (point 4.3.2.2).

## 4.3 SELECTION OF THRESHOLD VALUES IN THE ABSENCE OF FRENCH VALUES FOR LAND USE PLANNING

### 4.3.1 SECOND STEP: CRITICAL ANALYSIS

The second step consists in a critical analysis of the available data:

- ✓ For the AEGLs, critical analysis of key studies is performed in the available technical support documents (TSD), there is no reason to question them.
- ✓ For the ERPGs and IDLHs, a critical analysis of the key studies and/or their data should be conducted.

The critical analysis for ERPGs and IDLHs consists of evaluating the reliability, relevance and usefulness of the data.

For all thresholds, the selection of the key study is not questioned. These analyses are a tool to help in selecting the values for which reports are not always available, such as IDLH (the key studies may be cited as a reference or not).

It should be noted that this step requires toxicology training. If no particular toxicology skill is available, only the determination of level 3 is relevant or even level 2 if the required exposure time is only one hour or one half-hour.

### 4.3.2 THIRD STEP: SELECTION

After having reviewed the available values and, if applicable, conducted a critical analysis of the key studies and/or data, the third step, broken down into 4 levels, consists in making a selection from the available values according to the toxicological skills of the analyst and the analysis (or not) of the key study.

The third step consists of two separate parts depending on the available thresholds:

- ✓ If the AEGLs, ERPGs and IDLH thresholds are available, levels 1, 2 or 3 should be followed to determine or select thresholds (part 4.3.2.1).
- ✓ If the AEGLs and ERPGs thresholds are not available, one should follow (part 4.3.2.2):
- ✓ if the IDLH threshold is not available, level 4 based on the source data from the TEELs;
- ✓ if the IDLH threshold is available, level 4 for lethal effects based on the source data from the TEELs and the IDLH; and level 1 or 2 for irreversible effects thresholds using the IDLH value.

During this step, a toxicity analysis for the relevant substance must also be performed in order to identify the type of toxic effect (either systemic or local) and to show that there is a dose-effect relationship.

A flow chart (selection for land use planning) is proposed below as conclusion.

**N.B.** One should:

- ✓ calculate the saturated vapor concentration[11] in order to ensure that none of the threshold values used exceed it;
- ✓ ensure consistency of the set of provisional thresholds obtained with each other and with the available toxicological data.

[11] Calculation with the ideal gas law: C = (MM x P) / (R x T)
C: concentration at saturation (in $g.m^{-3}$)
MM: molar mass (in $g.mol^{-1}$)
P: vapor pressure (in Pa)
R: ideal gas constant (8,314 $J.mol^{-1}.K^{-1}$)
T: temperature in Kelvin : (273 + ℃)K

#### 4.3.2.1 THE AEGLS, ERPGS OR IDLH ARE AVAILABLE

This is the preferred process. Setting of three levels could be made. These levels are based on the analysis of the key study, knowledge of the dose-effect relationship and a selection by default, respectively. Determinations via level 1 and *via* part of level 2 require toxicological training.

**Reminder**:

- ✓ if no toxicology skills are available, only the determination of level 3 is relevant or level 2 if the required exposure time is only one hour (direct use of the ERPGs) or one half-hour (direct use of the IDLH);
- ✓ the selection of the key study by the reference organism is not questioned.

**DETERMINATION OF THE LETHAL EFFECTS THRESHOLDS**

*Determination of level "1"*

Ideally, one should perform one's own determination of the SPELs and SELSs by referring to the original publication of the AEGL-3 derivation or, failing this, the ERPG-3. The mortality data identified, may be used to perform a statistical analysis as proposed in the French methodology (www.ineris.fr, acute toxicity threshold studies and research/reports).

With this calculation of level 1 it is thus possible to propose threshold values for 1% (SPEL) and 5% (SELS) lethal effects.

*Determination of level "2"*

A less restrictive default value is the use of the ERPG-3, but which is only available for a single exposure time and requires extrapolation according to Haber's law $C^n.t = k$ with $n = 1$, for durations longer than one hour, or 3 for durations shorter than one hour, as described in the French methodology (cf. description of the selection of n in paragraph 3.5.1.1).

In the case where a threshold is sought only for an exposure time of one hour, it is possible to make a selection without modeling and without analyzing the key study, while also being aware of the limits unique to the selected threshold. The threshold to be considered is the ERPG-3.

This approach only makes it possible to propose threshold values for 1% (SPEL) lethal effects.

*Determination of level "3"*

This involves making a selection without modeling and without analyzing the key study, while being aware of the limits to the selected threshold. The thresholds to be considered are the AEGL-3.

The AEGLs, although scientifically more robust, are over protective, in the context of land use planning because they take into account susceptible sub-populations.

This approach only makes it possible to propose threshold values for 1% lethal effects (SPEL).

**DETERMINATION OF THE IRREVERSIBLE EFFECTS THRESHOLDS**

*Determination of level "1"*

As for lethal effects, ideally reference should be made to the original publication for determining available irreversible threshold values such as AEGL-2, ERPG-2 or IDLH and the French methodology (www.ineris.fr, acute toxicity thresholds studies and research/reports) should be followed.

*Determination of level "2"*

The direct use of ERPG-2 or IDLH values is possible. Preference should be given to the use of the ERPG-2, and in a second time to the IDLH.

The value is retained as a point of departure making it possible, as for the lethal effects, to extrapolate the SEIs by applying Haber's law $C^n.t = k$ with $n = 1$, for durations longer than 60 minutes for the ERPG-2 and longer than 30 minutes for the IDLH, or 3 for durations shorter than 60 minutes for the ERPG-2 and 30 minutes for the IDLH, as described in the French methodology (cf. description of the selection of n in paragraph 3.5.1.1).

**N.B.** If the thresholds for lethal effects have been determined *via* level 1, the Haber value of n obtained for these effects must be used for extrapolating the POD of the irreversible effects to the other durations.

In order to be able to perform this extrapolation, it is necessary to start from available toxicological data and show that there is a dose-effect relationship; otherwise, the use of Haber's law is not possible.

In the case where a threshold is sought solely for an exposure time of one hour, it is possible to make a selection without modeling and without analyzing the key study, while being aware of the limits of the selected threshold. The threshold to be considered is ERPG-2.

It is also possible to consider using the IDLH when the exposure time to be considered is 30 minutes. This selection should not be used as a first approach.

*Determination of level "3"*

This involves making a selection without modeling and without analyzing the key study, while also being aware of the limits unique to the threshold. The thresholds to be considered are the AEGL-2.

The AEGLs, although scientifically more robust, are over protective, in the context of land use planning, because they take into account susceptible sub-populations.

**DETERMINATION OF REVERSIBLE EFFECTS THRESHOLDS**

*Determination of level "1"*

As for irreversible effects, ideally reference should me made to the available original publication for determining reversible threshold values such as AEGL-1 and ERPG-1 and the French methodology (www.ineris.fr, acute toxicity thresholds studies and research/reports) should be followed.

*Determination of level "2"*

The direct use of the ERPG-1 is possible. This value is selected as a point of departure (POD[12]) making it possible, as for lethal and irreversible effects, to extrapolate SEIs by applying Haber's law $C^n.t = k$ with n = 1 for durations longer than one hour, or 3 for durations shorter than one hour, as described in the French methodology (cf. description of the selection of n in paragraph 3.5.1.1).

**N.B.** If the lethal effects thresholds have been determined *via* level 1, the Haber value of n obtained for these effects must be used for extrapolating the POD of the reversible effects to other durations.

In order to be able to perform this extrapolation, it is necessary, from toxicological data, to show that a dose-effect relationship exists; otherwise the use of Haber's law is not possible.

In the case where a threshold is sought solely for an exposure time of one hour, it is possible to make a selection without modeling and without analyzing the key study, while being aware of the limits unique to the selected threshold. The threshold to be considered is the ERPG-1.

*Determination of level "3"*

This involves making a selection without modeling and without analyzing the key study while being aware of the limits unique to the selected threshold. The thresholds to be considered are the AEGL-1.

AEGLs, although scientifically more robust, are protective, and regulatory context of urbanization control, due to the taking into account of susceptible populations.

#### 4.3.2.2 ONLY TEELS AND/OR THE IDLH ARE AVAILABLE

In the case where the IDLH is available, the thresholds for irreversible effects should be determined following step 3, level 1 or 2. Lethal effects will be achieved using level 4 below.

If only the TEELs are available, the lethal and irreversible effects will be achieved using level 4 below.

It is not possible to achieve reversible effects thresholds from this step.

[12] The POD is an effect observed for a given concentration/time pair

This level requires minimum toxicological training (notion of local effects[13], systemic effects[14], dose-effect relationship…).

*Determination of level "4"*

The TEELs have the advantage of being available for a number of values, but the quality and robustness of the source data used cannot be evaluated because the key studies are not cited, and only the NOAEL[15]/LOAEL[16] of these studies are described. This is why TEELs cannot be used directly, but rather some of their source data ($CL_0$, $CL_{01}$, $CL_{50}$).

The IDLH also has the advantage of reporting the source data used ($CL_{50}$ or $CL_0$) during its development.

All of these data should therefore be presented and some source data used in the order: $CL_{01}$, $CL_{50}$, $CL_0$. With these data it will be possible to determine the thresholds for lethal effects and irreversible effects. If several concentrations of the same type are available, the uppermost bound should be used.

With this approach it is possible to avoid seeking and evaluating all of the studies available in the literature in order to obtain lethal concentrations (the selection of the key study and therefore of its data by the reference organism is not questioned).

Particular attention must be paid to the exposure time. Indeed, in some cases, the development of these values is based on a NOAEL/LOAEL for durations longer than 24 hours. In this case, these values cannot be used as POD.

**SOURCE DATA: $CL_{01}$**

In order to obtain lethal effects thresholds, Haber's law should be applied with n=3 and n=1, respectively, for durations shorter or longer than the time of the POD of the key study.

In order to obtain irreversible effects thresholds, the lethal effects thresholds obtained above are used and divided by 9 in the case of a local acting chemical and by 27 in the case of a systemic acting chemical (see French Methodology).

[13] Effect of the substance at the point of contact (skin, eyes, respiratory tract). This is an irritating or corrosive effect.
[14] Effect of the substance, after diffusion and distribution in the organism, in other parts of the body where it performs its toxic action.
[15] The NOAEL is the highest dose of a substance for which no harmful effects are observed.
[16] The LOAEL is the lowest dose of a substance which causes harmful changes distinct from those observed in control animals.

**SOURCE DATA: $CL_{50}$**

In order to obtain lethal effects thresholds, Haber's law should be applied with n=3 and n=1, respectively, for durations shorter or longer than the time of the POD of the key study. These values should be divided by 3.5 in the case of a local acting chemical and by 10.5 in the case of a systemic acting chemical.

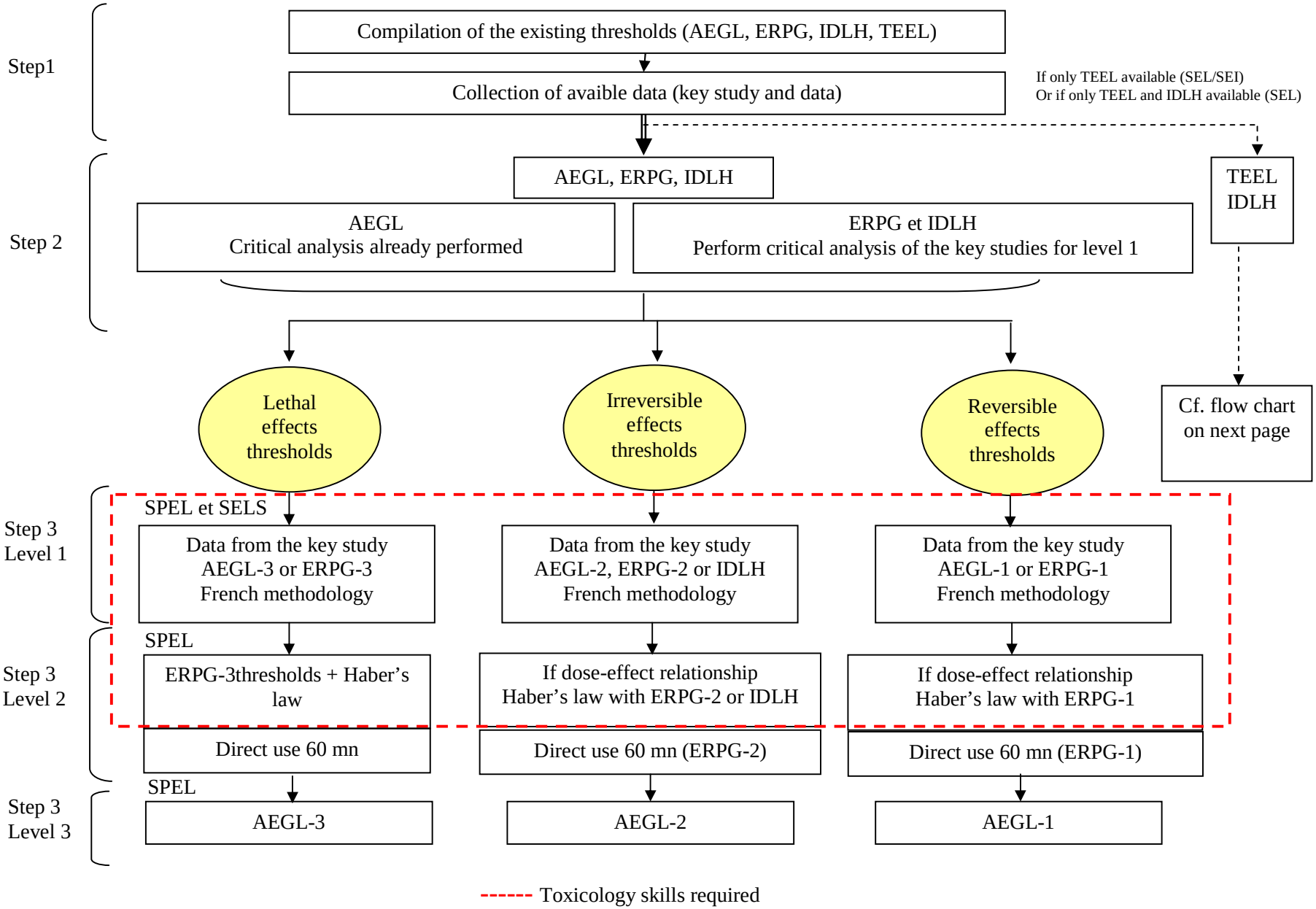
In order to obtain irreversible effects thresholds, the lethal effects thresholds obtained above are used and divided by 3 in the case of a local acting chemical and by 9 in the case of a systemic acting chemical.

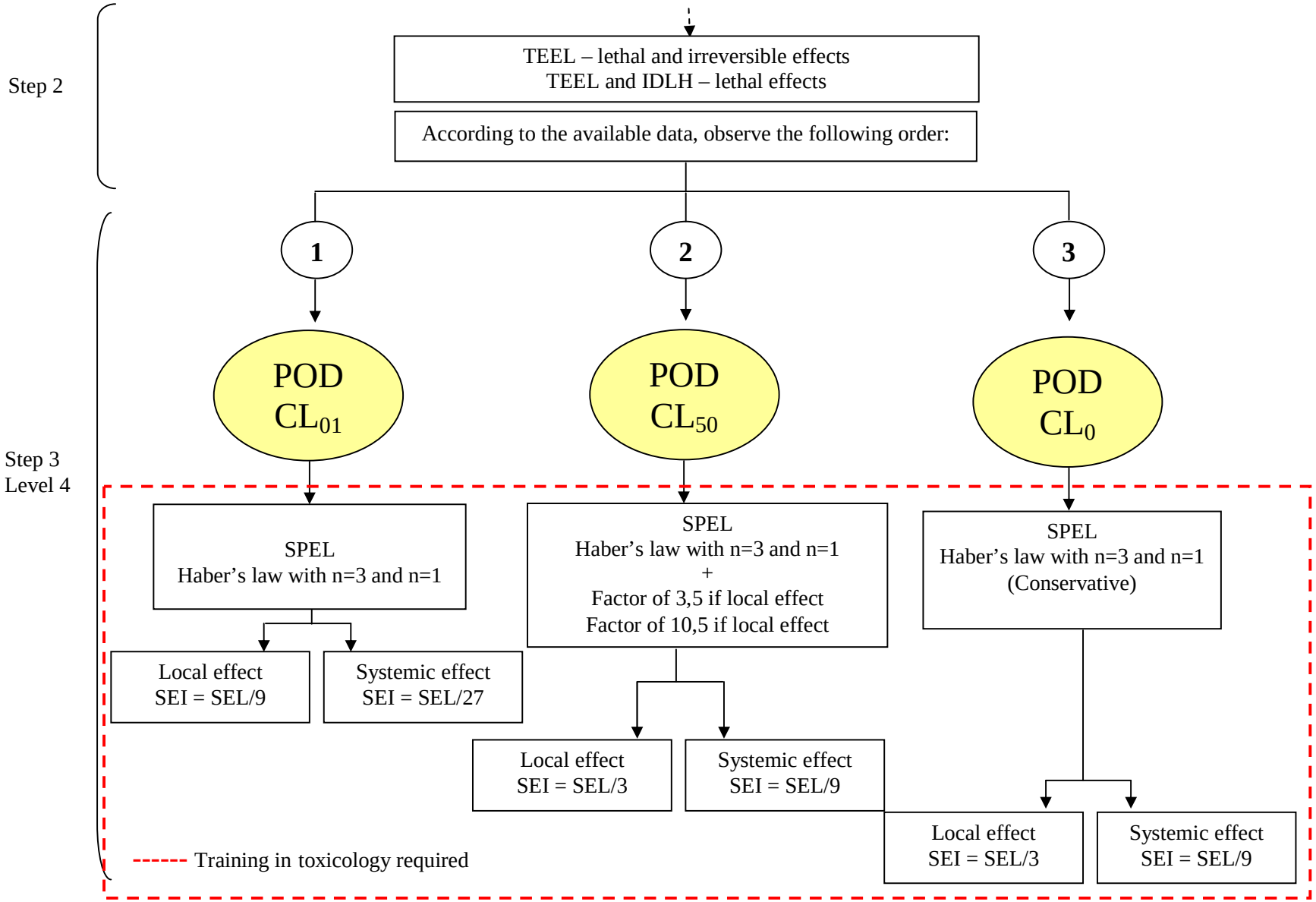
**SOURCE DATUM: $CL_0$**

In order to obtain lethal effects thresholds, Haber's law should be applied with n=3 and n=1, respectively, for durations shorter or longer than the time of the POD of the key study.

In order to obtain irreversible effects thresholds, the lethal effects thresholds obtained above are used and divided by 3 in the case of a local acting chemical and by 9 in the case of a systemic acting chemical.

#### 4.3.2.3 SUMMARY FLOW CHART FOR LAND USE PLANNING


Step1
Compilation of the existing thresholds (AEGL, ERPG, IDLH, TEEL)
Collection of avaible data (key study and data)
If only TEEL available (SEL/SEI)
Or if only TEEL and IDLH available (SEL)
Step 2
AEGL, ERPG, IDLH
TEEL
IDLH
AEGL
Critical analysis already performed
ERPG et IDLH
Perform critical analysis of the key studies for level 1
Lethal effects thresholds
Irreversible effects thresholds
Reversible effects thresholds
Cf. flow chart on next page
SPEL et SELS
Step 3 Level 1
Data from the key study AEGL-3 or ERPG-3 French methodology
Data from the key study AEGL-2, ERPG-2 or IDLH French methodology
Data from the key study AEGL-1 or ERPG-1 French methodology
SPEL
Step 3 Level 2
ERPG-3thresholds + Haber's law
If dose-effect relationship Haber's law with ERPG-2 or IDLH
If dose-effect relationship Haber's law with ERPG-1
Direct use 60 mn
Direct use 60 mn (ERPG-2)
Direct use 60 mn (ERPG-1)
SPEL
Step 3 Level 3
AEGL-3
AEGL-2
AEGL-1
Toxicology skills required


Step 2
TEEL – lethal and irreversible effects
TEEL and IDLH – lethal effects
According to the available data, observe the following order:
1
2
3
Step 3
Level 4
POD $CL_{01}$
POD $CL_{50}$
POD $CL_0$
SPEL
Haber's law with n=3 and n=1
SPEL
Haber's law with n=3 and n=1
+
Factor of 3,5 if local effect
Factor of 10,5 if local effect
SPEL
Haber's law with n=3 and n=1
(Conservative)
Local effect
SEI = SEL/9
Systemic effect
SEI = SEL/27
Local effect
SEI = SEL/3
Systemic effect
SEI = SEL/9
Local effect
SEI = SEL/3
Systemic effect
SEI = SEL/9
Training in toxicology required

## 4.4 SELECTION OF THRESHOLD VALUES IN THE ABSENCE OF FRENCH VALUES FOR EMERGENCY SITUATIONS

In emergency situations, the rescuers and intervention actors of a crisis cell do not have the time to conduct an in-depth review of the available literature. In that case, only step 1 (review of internet sites) should be performed in order to collect all of the available threshold values. A quick selection then has to be made based on recognizing the organisms having developed the acute toxicity thresholds.

For each new critical effect level, the following recommendations may be made.

### 4.4.1 SECOND STEP: SELECTION

#### 4.4.1.1 SELECTION OF VALUE(S) FOR THE LETHAL EFFECTS (SPEL)

The value whose definition appears most appropriate for an emergency / accidental situation is ERPG-3, which should be used as first approach.

The more conservative AEGL-3 values are to be considered either secondly, or when knowledge of the topography of the accident shows the presence of susceptible populations such as, for example, children or elderly persons. The TEEL-3 value could be used by default at last resort.

#### 4.4.1.2 SELECTION OF VALUE(S) FOR IRREVERSIBLE EFFECTS

As for lethal effects, preference must be given to the available ERPG-2 provided that certain so-called susceptible populations are not present within the perimeter of the accident.

In this case, the preferred values are AEGL-2, followed by the IDLH and TEEL-2 values, which are only to be used, in that order, by default at last resort.

#### 4.4.1.3 SELECTION OF VALUE(S) FOR REVERSIBLE EFFECTS

As for land use planning preference must be given to the AEGL-1 values which are, by definition, the closest to the SERs. In second place, the ERPG-1, then the TEEL-1 may be used.

### 4.4.2 IMPORTANT COMMENTS

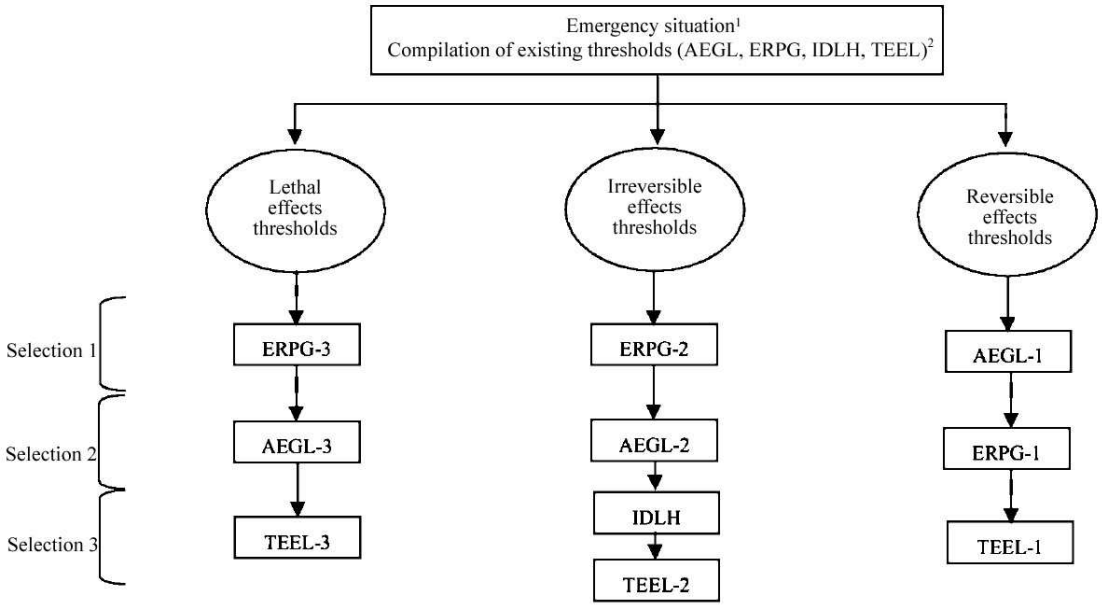
During these situations and during toxicological analysis, several points must be kept in mind:

- ✓ this is a quick selection in first stepwise approach. If the emergency situation persists, determination of the most relevant threshold should be based on a toxicological assessment with regard to its definition, the data which were used for its development (key study…) and to the situation on the site;

- ✓ the firefighters use VME (average exposure values) and VLE (short-term exposure limiting values) thresholds during their operations. These thresholds are used for developing the operational perimeter and cannot in any case be used for defining a safety perimeter regarding the population;

- ✓ the VSTAFs are not developed for emergency situations; these values should thus be used with caution in these situations. The AEGLs and ERPGs are preferred to them.

### 4.4.3 SUMMARY FLOW CHART IN EMERGENCY SITUATION




[1]: this is a quick selection as first approach. If the emergency situation persists, a toxicological assessment should be used as the basis for determining the most relevant threshold in terms of its definition, the data which were used for its development (key study…) and the situation on the site.

[2]: the VSTAFs are not developed for emergency situations; these values should thus be used with caution in these situations.

NB: the fire departments use the VME (Average Exposure Value) and VLE (short-term limit exposure value) thresholds during their operation. These thresholds are used for developing the operational perimeter and cannot under any circumstances be used for defining the safety perimeter with regard to the population.

# 5. SUMMARY

This guidance document proposes stepwise approaches which may be modulated according to toxicological training of the operator and available data:

- ✓ with toxicological training, the determination of thresholds must be done following the French methodology. If this determination is not possible, with the approaches proposed in this guidance document it is possible to obtain thresholds for informational purposes only;

- ✓ in the absence of toxicological training, step 1 (inventory of existing values), then step 3 level 2 (one part) or 3, which consists of identifying the existing values "closest" to the case studied, should be performed;

The table below shows the threshold values to be used in the absence of toxicological training:

| | **Exposure time (min)** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **10** | **20** | **30** | **60** | **120** | **240** | **480** |
| **SELS (SEL 5%)** | - | - | - | - | - | - | - |
| **SPEL (SEL 1%)** | AEGL-3 | - | AEGL-3 | ERPG-3<br>AEGL-3 | - | AEGL-3 | AEGL-3 |
| **SEI** | AEGL-2 | - | AEGL-2<br>(IDLH) | ERPG-2<br>AEGL-2 | - | AEGL-2 | AEGL-2 |
| **SER** | AEGL-1 | - | AEGL-1 | ERPG-1<br>AEGL-1 | - | AEGL-1 | AEGL-1 |

Table 2: Threshold values to be used in the absence of toxicological training

In order to determine values within the scope of an emergency situation, the principles of part 4.4 apply. It is underlined that if the emergency situation persists, toxicological analysis should be used as the basis for determining the most relevant threshold considering its definition, the data which were used for its development (key study…) and the situation on the site.

**N.B.** The same origins for the thresholds setting should be kept for the different effects levels (thus the ERPG-3 cannot be mixed and/or used with AEGL-2…).

# LIST OF APPENDICES

| Reference | Name | Number of pages |
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| Appendix 1 | Examples of selection of threshold values in the absence of French values for LUP<br>Comparison of provisional thresholds with the French thresholds<br>Bromine | 9 |
| Appendix 2 | Examples of selection of threshold values in the absence of French values for LUP<br>Comparison of provisional thresholds with the French thresholds<br>Methyl acrylate | 5 |
| Appendix 3 | Examples of selection of threshold values in the absence of French values for LUP<br>Comparison of provisional thresholds with the French thresholds<br>Acrylonitrile | 5 |

# Appendix 1

## Example of selection of threshold values in the absence of French values for land use planning

## Comparison of provisional thresholds with the French thresholds

## Bromine

Provisional thresholds are obtained for bromine according to the technical guidance document for selecting acute toxicity threshold values in case of the absence of French values.

The obtained provisional thresholds, with or without training of toxicology, are compared with the French thresholds.

## 1 – Development of provisional thresholds with training in toxicology

Step 1 – Review

For bromine, there are four types of thresholds: AEGL, ERPG, IDLH, TEEL.

Step 2 – Critical analysis

***AEGL***

The available AEGL thresholds are:

| | **10 minutes** | **30 minutes** | **1-hour** | **4-hours** | **8-hours** |
|---|---|---|---|---|---|
| **AEGL-1 (ppm)** | 0.033 | 0.033 | 0.033 | 0.033 | 0.033 |
| **AEGL-2 (ppm)** | 0.55 | 0.33 | 0.24 | 0.13 | 0.095 |
| **AEGL-3 (ppm)** | 19 | 12 | 8.5 | 4.5 | 3.2 |

The AEGL-1 and -2 values are based on the study by Rupp and Henschler (1967). This study is available in German, but the abstract is in English:

- ✓ **Number of volunteers**: 20 students (male) in good health

- ✓ **Experimental conditions:**

The bromine vapors were generated from a liquid solution contained in a 2 L heating flask and diluted with fresh air in an 8 $m^3$ chamber. The concentrations were determined by titrimetry using a thiosulfate solution for high concentrations and by spectrophotometry for concentrations below 0.01 ppm. The samples were collected via a potassium iodide solution for high concentrations and by absorption of o-toluidine hydrochloride for low concentrations.

The students were not informed of the type of gas, concentration levels and possible effects.

In order to study symptoms of irritation, the students entered the exposure chamber in groups of 3 to 4 people and indicated, every 5 minutes, the effects they experienced (subjective data).

- ✓ **Exposure concentration**: 0 to 0.9 ppm (for irritation symptoms)
- ✓ **Exposure time**: 30 minutes
- ✓ **Observation time:** -
- ✓ **Control group**: yes
- ✓ **Results**:

  Ocular irritation was the first effect noted for a concentration of 0.1 ppm. It generally occurred during the first 30 minutes.

  From 0.2 ppm and for all concentrations above that level, ocular, respiratory tract and nasal irritation were observed. These effects increased rapidly with the concentration.

  Between 0.5 and 0.9 ppm, an exposure of 5 minutes was perceived as uncomfortable. However, the intensity of the effects (nasal, respiratory and ocular irritation) did not increase with the concentration

It should be noted that the authors considered that the actual concentrations are approximately 40% (17 to 57%) lower than the concentrations reported here. Indeed, the measurements were performed close to walls and not in the air close to the volunteers. Furthermore, the concentrations depend on the number of people entering the room (variation due to inhaled volumes) and the air renewal rate in the room (22 times per hour using a fan).

The AEGL-3 are based on the study by Schlagbauer and Henschler (1967). This study is available in German, but the abstract is in English:

- ✓ **Studied species**: NMRI mouse
- ✓ **Experimental conditions**: same measurement and bromine generation methods as Rupp and Henschler (1967) were used.
- ✓ **Exposure concentration**:
  1st experiment: 111—140 – 200 – 236 – 252 – 268 – 290 – 315 ppm
  2nd experiment: 22 and 44 ppm
- ✓ **Exposure time**:
  1st experiment: 30 minutes
  2nd experiment: 3 and 6 hours

- ✓ **Observation time:**
  1st experiment: 10 days
  2nd experiment: 10 days

- ✓ **Sex and number of animals per group**: 10 non pregnant female mice

- ✓ **Control group**: no

- ✓ **Results**:

1st experiment: for an exposure of 30 minutes, a $CL_{50}$ of 174 ppm and a $CL_{01}$ of 116 ppm were determined.

| Concentration (ppm) | Mortality (days of observation) | | |
|---|---|---|---|
| | 0 to 2 | 2 to 4 | total to 10 |
| 111 | 0/10 | 0/10 | 0/10 |
| 140 | 0/10 | 3/10 | 3/10 |
| 200 | 2/10 | 4/10 | 6/10 |
| 236 | 2/10 | 5/10 | 9/10 |
| 252 | 4/10 | 7/10 | 10/10 |
| 268 | 5/10 | 7/10 | 9/10 |
| 290 | 7/10 | 9/10 | 10/10 |
| 315 | 9/10 | 10/10 | 10/10 |

2nd experiment:

| Concentration (ppm) | Exposure time (hours) | Mortality (days of observation) | | |
|---|---|---|---|---|
| | | 2 | 4 | 10 |
| 40 | 6 | 4/10 | 6/10 | 8/10 |
| | 3 | 2/10 | 3/10 | 3/10 |
| 22 | 6 | 2/10 | 4/10 | 7/10 |
| | 3 | 0/10 | 0/10 | 0/10 |

***ERPG***

The available ERPG thresholds are:

ERPG-1: 0.1 ppm

ERPG-2: 0.5 ppm

ERPG-3: 5 ppm

There is no information relating to the development methodology (key study…).

***IDLH***

The available IDLH (1994) is 3 ppm.

The key studies for IDLH are either monographs or summaries, and therefore cannot be used (lack of data, data lacking details…).

The IDLH value of 1987 (10 ppm) is based on the AIHA study (1958) which indicates that concentrations above 10 ppm cause severe irritation of respiratory airways. The AIHA (1958) cites the study by Henderson and Haggard (1943) which reports that concentrations from 40 to 60 ppm are dangerous for humans.

The IDLH value was revised based on the study by Flury and Zernick (1931) which reports that a concentration of 0.75 ppm causes effects for an exposure of 6 hours.

***TEEL***

The available TEEL thresholds are:

TEEL-0: 0.033 ppm

TEEL-1: 0.033 ppm

TEEL-2: 0.24 ppm

TEEL-3: 8.5 ppm

The TEEL 1, 2 and 3 values correspond to the AEGL values.

Step 3 – Selection

Starting from the available thresholds, the selection guide recommends:

- ✓ to determine the lethal effects, using the key study from AEGL-3. The SELSs will be able to be determined.

- ✓ to determine the irreversible effects, using the AEGL-2 key study. But this key study only indicates reversible effects (irritation), and therefore does not correspond to the criteria required for use in the framework of the methodology for developing the French acute toxicity threshold values. It cannot be retained.

As the IDLH key study is not very detailed, it also cannot be used.

The guidance document therefore recommends using the ERPG-2 value.

Due to development *via* different threshold values, the consistency of the provisional thresholds should be verified.

*Toxicological data for bromine*

Bromine is a brown-red liquid with a pungent odor, denser than water and water-soluble. Cold, it emits abundant suffocating vapors.

Bromine is non-combustible, but as it is very reactive with organic or mineral products, it may cause fires or explosions.

Bromine presents local toxicity: it is a strong respiratory irritant and may cause pulmonary edemas. The penetration kinetics *via* the pulmonary route, in animals and humans, are probably not very different, since bromine reacts very quickly at the exposure site.

Due to its irritating action, Haber's law may be used.

The concentration at saturated vapor at 20º C is 1,530 $mg.m^{-3}$, or 230,000 ppm.

***SEL***

*Level 1*

This quantitative analysis was carried out from the key study of the AEGL-3 values (the selection of key study for the AEGL thresholds is not questioned).

As the selected study provides several duration/concentration pairs, the statistical model used is the "standard probit" model. By probit analysis, the proportion of effects (here mortality) may be linked to the exposure level, characterized by a concentration and a duration.

The probability of the substance causing a harmful effect (mortality) can be written:

$$p = F\left(\frac{\log(C) + m\log(\tau) - \mu}{\sigma}\right)$$

*p* is therefore the probability of an individual chosen at random and exposed to a concentration C of substance for a time $\tau$ having a response (mortality). The hypothesis of this model is that an individual's tolerance for a chemical substance is distributed according to a normal (Gaussian) law within the general population.

F is the distribution function of the normal law. It is written as:

$$F(x) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{x}\exp\left(-\frac{t^2}{2}\right)dt$$

In order to make this mathematical modeling, the following data are needed:

- ✓ *B*: the number of groups of animals (or individuals)
- ✓ $C_i$: the exposure concentration for the animals in the group *i*

- ✓ $b_i$: the number of animals (or individuals) in the group *i* and exposed to the concentration $C_i$
- ✓ $y_i$: the number of animals (or individuals) affected by the treatment from among the $n_i$ exposed to the concentration $C_i$
- ✓ $T_i$: the exposure time of the group *i.*

The calculation of the $CL_{50}$, $CL_{05}$ and $CL_{01}$ depending on the exposure time was based on the estimation of the regression parameters (m, $\mu$ and $\sigma$) thereby obtained through a Bayesian analysis. The confidence intervals are determined under the hypothesis of a binomial likelihood function [FINNEY (1971)].

One write:

$$\mathbf{CL1\% = \exp(\mu - 2.33\sigma - m\log(\tau))}$$
$$\mathbf{CL5\% = \exp(\mu - 1.645\sigma - m\log(\tau))}$$
$$\mathbf{CL50\% = \exp(\mu - m\log(\tau))}$$

By using the (MCSim®) statistics software package, the parameters may be obtained for the probit equations.

Finally, the value *n* of the Haber relationship ($C^n.t = k$) was also calculated from analyzed and selected data.

The established probit equation and the corresponding value *n*, for the study by Schlagbauer and Henschler (1967), is the following one:

$$Y = 3.15\ \ln(\text{concentration}) + 2.45\ \ln(\text{time}) - 24.48$$
$$n = 1.28 \qquad \text{IC95 } [1.15 - 1.50]$$

Y is a function of the probit equation.

| **$CL_{01}$ (ppm)** | | **$CL_{05}$ (ppm)** | |
|---|---|---|---|
| **Time (min)** | | **Time (min)** | |
| 1 | 1146 | 1 | 1425 |
| 10 | 190 | 10 | 236 |
| 20 | 111 | 20 | 138 |
| 30 | 81 | 30 | 100 |
| 60 | 47 | 60 | 58 |
| 120 | 27 | 120 | 34 |
| 240 | 16 | 240 | 20 |
| 480 | 9 | 480 | 12 |

As bromine presents local toxicity and the key study is conducted in rats (most susceptible species for respiratory tract irritants), no uncertainty factor was used.

The SELs obtained are:

| TIME (min) | SELS | | SPEL | |
|---|---|---|---|---|
| | mg/m$^3$ | ppm | mg/m$^3$ | ppm |
| 1 | 9,405 | 1,425 | 7,564 | 1,146 |
| 10 | 1,558 | 236 | 1,254 | 190 |
| 20 | 911 | 138 | 733 | 111 |
| 30 | 660 | 100 | 535 | 81 |
| 60 | 383 | 58 | 310 | 47 |
| 120 | 224 | 34 | 178 | 27 |
| 240 | 132 | 20 | 106 | 16 |
| 480 | 79 | 12 | 59 | 9 |

***SEI***

*Level 2*

The ERPG-2 value is used as the point of departure for extrapolation to the other durations by applying Haber's law ($C^n.t = k$) with Haber's n defined during the development of the lethal effects (n=1.28).

The SEIs obtained are:

| Time (min) | SEI (ppm) |
|---|---|
| 1 | 12 |
| 10 | 2 |
| 20 | 1 |
| 30 | 0.8 |
| 60 | **0.5** |
| 120 | 0.29 |
| 240 | 0.17 |
| 480 | 0.1 |

Conclusion and coherence of the thresholds

The different thresholds (SELS, SPEL and SEI) are consistent with each other.

If we compare the provisional thresholds with the thresholds determined by the French experts group, the SELs are identical (same key study) and the provisional SEIs are upper .

| TIME (min) | Provisional thresholds | | | Thresholds determined by the experts group | | |
|---|---|---|---|---|---|---|
| | SELS | SPEL | SEI | SELS | SPEL | SEI |
| | ppm | ppm | ppm | ppm | ppm | ppm |
| 1 | 1,425 | 1,146 | 12 | 1,425 | 1,146 | 127 |
| 10 | 236 | 190 | 2 | 236 | 190 | 21 |
| 20 | 138 | 111 | 1 | 138 | 111 | 12 |
| 30 | 100 | 81 | 0.8 | 100 | 81 | 9 |
| 60 | 58 | 47 | **0.5** | 58 | 47 | 5 |
| 120 | 34 | 27 | 0.29 | 34 | 27 | 3 |
| 240 | 20 | 16 | 0.17 | 20 | 16 | 2 |
| 480 | 12 | 9 | 0.1 | 12 | 9 | 1 |

**2 – Development of provisional thresholds without training in toxicology**

Step 1 – Review

For bromine, there are four types of thresholds: AEGL, ERPG, IDLH, TEEL.

Step 2 – Critical analysis

No critical analysis is possible (lack of training in toxicology).

Step 3 – Selection

***SEL***

*Level 2*

The ERPG threshold is selected for an exposure time of one hour.

*Level 3*

The AEGL thresholds are selected.

***SEI***

*Level 2*

The ERPG threshold is selected for an exposure time of one hour.

The IDLH threshold may be used for an exposure time of one half-hour.

*Level 3*

The AEGL thresholds are selected.

**N.B.** The same origins for the thresholds should be kept for the different effects levels (thus the ERPG-3 cannot be mixed and/or used with AEGL-2…).

## 3 – Bibliography


AIHA [1958]. Bromine. In: Hygienic guide series. Am Ind Hyg Assoc J *19*:349-350.

Flury F, Zernik F [1931]. Schädliche Gase Dämpfe, Nebel, Rauch- und Staubarten. Berlin, Germany: Verlag von Julius Springer, p. 538 (in German).

Henderson Y, Haggard HW [1943]. Noxious gases. 2nd ed. New York, NY: Reinhold Publishing Corporation, p. 133.

ILO [1971]. Bromine. In: Encyclopedia of occupational health and safety. 2nd ed. Vol. I (A-K). Geneva, Switzerland: International Labor Office, p. 211.

MCA [1968]. Chemical safety data sheet SD-49: properties and essential information for safe handling and use of bromine. Washington, DC: Manufacturing Chemists Association, pp. 1-18.

NFPA [1978]. Fire protection guide on hazardous materials. 7th ed. Boston, MA: National Fire Protection Association, p. 49-65.

Rupp H. and Henschler D., 1967. Wirkungen geringer Chlor- und Bromkonzentrationen auf den Menschen. Int. Archiv für Gewebepathologie und Gewerbehygiene 23: 79-90.

Schalgbaer M. And Henschler D., 1967. Toxicität von Chlor und Brom bei einmaliger und wiederholter Inhalation. Int. Archiv für Gewebepathologie und Gewerbehygiene 23: 91-98.

# Appendix 2

## Examples of selection of threshold values in the absence of French values for land use planning
## Comparison of provisional thresholds with the French thresholds
## Methyl acrylate

## 1 - Development of provisional thresholds with training in toxicology

Step 1 – Review

For methyl acrylate, there are two types of thresholds: IDLH and TEEL.

Step 2 – Critical analysis

***IDLH***

The available IDLH value (1994) is 250 ppm.

The IDLH 87 is developed from the study by Smyth and Carpenter (1948) cited by Patty (1963). This is a study on rats from which a $CL_{50}$ of 1,350 ppm for an exposure time of 4 hours was defined (3 rats dead out of 6).

Using the method for developing IDLH, a value of 1,000 ppm is obtained.

The IDLH was revised, in 1994, based on three studies:

- ✓ Oberly and Tansey (1985) which indicates a $CL_{50}$ of 1,350 ppm for an exposure time of 4 hours in rats (3 dead rats out of 6).
- ✓ Smyth and Carpenter (1948) which indicates a $CL_{50}$ of 1,000 ppm for an exposure time of 4 hours in rats.
- ✓ Treon *et al*. (1949) Schaefer (1951) which indicates a $CL_{50}$ of 2,522 ppm for an exposure time of one hour in rabbits.

The revised value is 250 ppm.

***TEEL***

The available TEEL thresholds are:

TEEL-0: 2 ppm

TEEL-1: 2 ppm

TEEL-2: 7.5 ppm

TEEL-3: 150 ppm

No basic data are available.

Step 3 – Selection

Starting from the available thresholds, the current guidance document recommends:

- for lethal effects, using the base data for the TEEL values or the IDLH value. The SELS will not be determined.
- for irreversible effects, using the IDLH value (the raw value or the key study).

The consistency of the thresholds should be verified.

Toxicological data for methyl acrylate

Methyl acrylate is a colorless liquid. It is a flammable liquid, the vapors of which may form explosive mixtures with air. The vapors may polymerize, right from room temperature, when not suitably inhibited.

The described toxic effects are in favor of mainly local toxicity. The substance is very irritating for the eyes, skin and mucosa. It is quickly absorbed by tissues, even by unbroken skin. Inhalation of the substance may cause pulmonary edema.

Due to its irritating action, Haber's law may be used.

Furthermore, we have:

- The saturated vapor concentration at 20° C is 320 $mg.l^{-1}$ or 90,000 ppm;
- The explosive limits are from 2.8% (LEL) to 25% (UEL).

***SEL***

*Level 4*

The TEEL values and the IDLH value give several $CL_{50}$:

| Species | Reference | $CL_{50}$ | Exposure time |
|---|---|---|---|
| Rat | Oberley and Tansey, 1985 | 1,350 | 4 hours |
| Rat | Smyth and Carpenter, 1948 | 1,000 | 4 hours |
| Rabbit | Treon *et al.*, 1949 | 2,522 | 1 hour |

The lowest value is selected (a $CL_{50}$ in rats for an exposure time of 4 hours of 1,000 ppm). Applying Haber's law (with n=3 for durations shorter than 4 hours and n=1 for durations longer than 4 hours) and, due to local toxicity, dividing by 3.5, the following thresholds are obtained:

| Time (min) | $CL_{50}$ (Haber's law) | SPEL |
|---|---|---|
| 1 | 6,214 | 1,776 |
| 10 | 2,884 | 824 |
| 20 | 2,289 | 654 |
| 30 | 2,000 | 571 |
| 60 | 1,587 | 454 |
| 120 | 1,260 | 360 |
| 240 | **1,000** | **286** |
| 480 | 500 | 143 |

***SEI***

*Level 1*

The reference for the IDLH key study is incomplete; it therefore cannot be used by applying the French methodology.

*Level 2*

Applying Haber's law, with n=3 and n=1, to the IDLH value, which is therefore used as the point of departure (POD). The following thresholds are obtained:

| Time (min) | SEI |
|---|---|
| 1 | 777 |
| 10 | 361 |
| 20 | 286 |
| 30 | **250** |
| 60 | 125 |
| 120 | 62 |
| 240 | 31 |
| 480 | 16 |

Conclusion and consistency of the thresholds

The thresholds obtained are consistent with each other (SPEL and SEI).

If we compare the provisional thresholds with the thresholds determined by the expert group, we see that the provisional SEL and the provisional SEI are upper.

| TIME (min) | Provisional thresholds | | Thresholds determined by the expert group | |
|---|---|---|---|---|
| | SPEL | SEI | SPEL | SEI |
| | ppm | ppm | ppm | ppm |
| 1 | 1,776 | 777 | 42,063 | 4,674 |
| 10 | 824 | 361 | 6,882 | 765 |
| 20 | 654 | 286 | 3,991 | 443 |
| 30 | 571 | 250 | 2,902 | 322 |
| 60 | 454 | 125 | 1,683 | 187 |
| 120 | 360 | 62 | 976 | 108 |
| 240 | 286 | 31 | 566 | 63 |
| 480 | 143 | 16 | 328 | 36 |

**2 – Development of provisional thresholds without training in toxicology**

Step 1 – Review

For methyl acrylate, there are two types of thresholds: IDLH and TEEL.

Step 2 – Critical analysis

No critical analysis is possible (absence of training of toxicology).

Step 3 – Selection

***SEL***

*Level 3*

No threshold can be selected.

***SEI***

*Level 3*

Only IDLH can be selected for an exposure time of one half-hour (250 ppm).

## 3 – Bibliography

Institut National de Recherche et de Sécurité (1987). Fiche toxicologique n° 181 – acrylate de méthyle.

Oberly R and Tansey MF (1985). $LC_{50}$ values for rats acutely exposed to vapors of acrylic and methacrylic acid esters. J Toxicol Environ Health *16*:811822.

Patty FA, ed. (1963). Industrial hygiene and toxicology. 2nd rev. ed. Vol. II. Toxicology. New York, NY: Interscience Publishers, Inc., p. 1880.

Smyth HF Jr and Carpenter CP (1948). Further experience with the rangefinding test in the industrial toxicology laboratory. J Ind Hyg Toxicol *30*:6368.

Treon JF, Sigmon H, Wright H and Kitzmiller KV (1949). The toxicity of methyl and ethyl acrylate. J Ind Hyg Toxicol *31*:317326.

# Appendix 3

## Examples of selection of threshold values in the absence of French values for land use planning

## Comparison of provisional thresholds with the French thresholds

## Acrylonitrile

## 1 – Development of provisional thresholds with training in toxicology

Step 1 – Review

For acrylonitrile, there are four types of thresholds: AEGL, ERPG, IDLH, TEEL.

Step 2 – Critical analysis

***AEGL***

The available AEGL thresholds are:

| | **10 minutes** | **30 minutes** | **one hour** | **four hours** | **eight hours** |
|---|---|---|---|---|---|
| **AEGL-1 (ppm)** | 4.6 | 4.6 | 4.6 | 4.6 | 4.6 |
| **AEGL-2 (ppm)** | 290 | 110 | 57 | 16 | 8.6 |
| **AEGL-3 (ppm)** | 480 | 180 | 100 | 35 | 19 |

As the technical document is in process, it is not available. Thus the key studies are not specified.

***EPRG***

The available EPRG thresholds are:

ERPG-1: 10 ppm

ERPG-2: 35 ppm

ERPG-3: 75 ppm

There is no information relating to the development methodology (key study…).

***IDLH***

The available IDLH (1994) is 85 ppm.

The IDLH 87 (500 ppm) is developed from the study by Carpenter *et al.* (1949) cited by Spector (1956). This study gives a $CL_{50}$ of 500 ppm in rats for an exposure time of 4 hours.

The revised IDLH value is based on the study by Schwanecke (1966) on volunteers. This study gives a $CL_0$ of 452 ppm for an exposure time of one hour.

This study is in German. Because of this, it cannot be used in the framework of the development methodology for the French acute toxicity threshold values.

***TEEL***

The available TEEL thresholds are:

TEEL-0: 2 ppm

TEEL-1: 4.6 ppm

TEEL-2: 57 ppm

TEEL-3: 100 ppm

TEEL 1, 2 and 3 values stem from the AEGL values.

Step 3 – Selection

From the available thresholds, the current technical guidance document recommends:

- ✓ to determine the lethal effects, using the value of the ERPG-3. The AEGL key study is not available.
- ✓ to determine the irreversible effects, using the ERPG-2 value. The AEGL and IDLH key studies are not available.

*Toxicological data for acrylonitrile*

Acrylonitrile is a colorless or yellowish liquid, which is very volatile and has a slightly pungent characteristic odor.

In humans, the major toxic effects of acrylonitrile are related to the release of cyanide ions which inhibit many enzymatic systems, in particular cytochrome oxidases, causing cellular asphyxia.

The available data in humans show that the pulmonary effects caused by acrylonitrile are equivalent in humans and animals. The modes of toxicity of this substance are close, but the metabolism shows variations in the extrapolation of animal data to humans.

Furthermore, it is emphasized that acrylonitrile is a substance which has a dual physiopathogenic impact. Indeed, it is characterized by effects on the central nervous system as well as by carcinogenic effects corresponding primarily to lung cancers in humans and tumors of the glial cells of the central nervous system in animals.

***SEL***

*Level 2*

The ERPG-3 (75 ppm) is therefore used as POD for the use of Haber's law with n=3 for durations shorter than one hour and n=1 for times longer than one hour.

The SPEL obtained are:

| Time (min) | SPEL (Haber's law) |
|---|---|
| 1 | 294 |
| 10 | 136 |
| 20 | 108 |
| 30 | 94 |
| 60 | **75** |
| 120 | 38 |
| 240 | 19 |
| 480 | 9 |

***SEI***

*Level 2*

We apply Haber's law, with n=3 and n=1, to the ERPG-2 value, which is therefore used as a point of departure (POD).

The SEI obtained are:

| Time (min) | SEI (Haber's law) |
|---|---|
| 1 | 137 |
| 10 | 64 |
| 20 | 50 |
| 30 | 44 |
| 60 | **35** |
| 120 | 18 |
| 240 | 9 |
| 480 | 4 |

Conclusion and coherence of the thresholds

The provisional thresholds, resulting from the same values (ERPG), are consistent with each other.

If we compare the provisional thresholds with the thresholds determined by the expert group, we see that the SEL are upper and the SEI are equivalent to the thresholds determined by the group of experts (generally, slightly more upper bound).

| TIME (min) | Provisional thresholds | | Thresholds determined by the expert group | |
|---|---|---|---|---|
| | SPEL | SEI | SPEL | SEI |
| | ppm | ppm | ppm | ppm |
| 1 | 294 | 137 | 3,070 | 486 |
| 10 | 136 | 64 | 542 | 85 |
| 20 | 108 | 50 | 320 | 50 |
| 30 | 94 | 44 | 236 | 37 |
| 60 | 75 | 35 | 139 | 22 |
| 120 | 38 | 18 | 82* | 13* |
| 240 | 19 | 9 | 49* | 8* |
| 480 | 9 | 4 | 29* | 4* |

* values determined by Haber's law but not determined in the INERIS report.

**2 – Development of provisional thresholds without training in toxicology**

Step 1 – Review

For acrylonitrile, there are four types of thresholds: AEGL, ERPG, IDLH, TEEL.

Step 2 – Critical analysis

No critical analysis is possible (absence of training of toxicology).

Step 3 – Selection

***SEL***

*Level 2*

The ERPG threshold is selected for an exposure time of one hour.

It is also possible to rely on the IDLH for an exposure time of one half-hour, but it is preferable to select the ERPG.

*Level 3*

The AEGL thresholds are selected.

***SEI***

*Level 2*

The ERPG threshold is selected for an exposure time of one hour.

*Level 3*

The AEGL thresholds are selected.

**N.B.** The same origins for the thresholds should be kept for the different effects (thus the ERPG-3 cannot be used with AEGL-2).

**3 – Bibliography**

Carpenter CP, Smyth HF Jr., Pozzani UC (1949). The assay of acute toxicity, and the grading and interpretation of results of 96 chemical compounds. J Ind Hyg Toxicol *31*(6):344.

Schwanecke R (1966). Safety hazards in the handling of acrylonitrile and methacrylonitrile. Zentralbl Arbeitsmed Arbeitsschutz *16*(1):1-3 (in German).

Spector WS, ed. (1956). Handbook of toxicology. Vol. I. Acute toxicities of solids, liquids and gases to laboratory animals. Philadelphia, PA: W.B. Saunders Company, pp. 322-323.