# Vinyl Chloride : acute toxicity thresholds in the context of controlling urban development or land use planning

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# VINYL CHLORIDE

## ACUTE TOXICITY THRESHOLDS IN THE CONTEXT OF CONTROLLING URBAN DEVELOPMENT OR LAND USE PLANNING

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The objective of this paper is to present, based on the example of vinyl Chloride , the french procedure to set acute toxicity thresholds in the context of controlling urban development or landuse planning.

Vinylchloride is a good example because it has never been until now examined for its **acute toxicity** and it is a carcinogenic chemical for humans chronically exposed at low concentration.

First it must be noted that these acute toxicity thresholds are established in a regulatory context (European Seveso II Directive , 1996)

A risk study uses accident scenarios combined with threshold effects in human beings exposed to chemicals agents in order to be able to calculate the extent of:

- zones of hazardous effects before and after reducing the risk at source,
- isolation zones for controlling urban development.

The risk and safety study leads to determine the distances of effects centred on the storage unit, namely:

- the "distance of lethal effects"
- the "distance of irreversible effects"

The definitions of the toxicity thresholds were laid down at a consultation meeting on 4 June 1998, between representatives of the government, INERIS and the chemical industry.(transparent)

"*Lethal effects*" are those which cause death in most individuals.

"*Irreversible effects*" correspond to a persistent injury or functional damage as a direct result of exposure in an accident situation (single, short-duration exposure resulting in disability).

"*Reversible effects*" are when there is a return to the state of health prior to the accident.

The "**lethal effects threshold**" is the maximum concentration of pollutant in the air for a given exposure time, below which no deaths are observed in most individuals.

The "**irreversible effects threshold**" is the maximum concentration of pollutant in the air for a given exposure time, below which no irreversible effects are observed in most individuals.

These thresholds were drawn up by a "groupe de consensus" following the "Methodology for determining lethal effects and irreversible effects thresholds" in the case of accidental release of a chemical substance into the atmosphere, which was adopted on 3rd May 2001 and may be consulted on the INERIS Internet site (www.ineris.fr).

The composition of the « groupe de consensus « includes persons coming form government, public organisations and industry

The main steps of the demarch are the following (transparent) :

- Research of available Official value
- Research and examination of the toxicity data in human beings
- Research and examination of the toxicity data in animals
- Analysis of toxicity data
    - Analysis of lethality data
    - Analysis of the non-lethal-effect
- Review of the results and definition of the acute thresholds levels

## 1. Concerning the Official data

TEELS (Temporary Exposure Emergency Limits ) are defined by the US Ministry of Transport and used when ERPGs are not available. They are intended for assessing the effects on a general population in the case of accidental exposure for a period of sixty minutes. They are defined without a safety factor and characterised (transparent)

For vinyl chloride, these thresholds are:

- TEEL-0: 10 ppm
- TEEL-1: 50 ppm

- TEEL-2: 50 ppm
- TEEL-3: 75 ppm

2. **A large review of the litterature** has been made to find the toxicity data for humans and animals.

3. Then the qualitative **analysis of the lethal** data has permitted to select two studies taking into account quality criteria.
   - **Mastromatteo** (1960)
   - **Prodan** (1978)

The quantitative analysis was carried out based on the studies selected .

The statistical model used is the probit model. The probit analysis enables the proportion of effects (here mortality) to be linked to the level of exposure, characterised by a concentration and a time period.

Statistics software (MCSim®) was used to obtain probit equations. The $LC_{50}$ and $LC_{01}$.were calculated.

The value *n* in Haber's equation ($C^n.t = k$) has also been calculated from the analysed and selected data.

For each animal species, the probit equation established and this value *n* are as follows: (transparent)

| | | |
|---|---|---|
| • Mice | Y = 7.3 ln(concentration) + 3.04 ln(time) – 99.8 | n = 7.3/3.04 = 2.4 |
| • Rats | Y = 7.39 ln(concentration) + 2.42 ln(time) – 99.9 | n = 7.39/2.42 = 3.05 |
| • Guinea Pigs | Y = 4.03 ln(concentration) + 1.58 ln(time) – 57.4 | n = 4.03/1.58 = 2.55 |

Y is a function of the probit equation.

Concentration is expressed in ppm and time in minutes.

For determining the non-lethal effects threshold according to the various studies analysed, the expert group examined the studies and critical effects from various studies (transparent)

4. **In the review of the results** it was considered that the data available for humans and animals show that the toxic mechanisms of this substance are the same and the pulmonary kinetics route do not differ significantly. This enables the animal data to be extrapolated easily to human beings.

➢ ***Definition of the lethal effects thresholds in human beings***

Analysis of the results on rat, mouse and guinea pig shows that the guinea pig is the most sensitive animal species. (transparent)

Thus, examining these results for these species combined with the data available in the literature enables us to adopt the data relating to mice for determining lethal effects thresholds (better quality of data). These thresholds are based on the values of $LC_{01}$ for exposure times of 1, 10, 20, 30 and 60 minutes.

The choice of data relating to mice is supported by the results of Mastromatteo's study (1960), which shows no mortality whatever the animal species (rat, mouse, guinea pig) at 100,000 ppm for 20 minutes.

Furthermore, Belej's study (1974) shows no toxicity in primates for exposures of five minutes to 200,000 ppm. There is therefore little or no difference between species, which justifies not applying a safety factor in extrapolating the data from animal to humans.

Finally, we should remember that the lethal effect induced by vinyl chloride is characterised by a narcotic effect depressing the central nervous system causing cerebral anoxia.

The values adopted are set out in the table below: (transparent)

| $LC_{01}$ | | |
|---|---|---|
| **Time (minutes)** | **$mg/m^3$** | **ppm** |
| 1 | 1,561,167 | 603,000 |
| 10 | 608,415 | 235,000 |
| 20 | 455,664 | 176,000 |
| 30 | 385,761 | 149,000 |
| 60 | 289,968 | 112,000 |

It should be underlined that these **lethal effects thresho**lds are in the high flammability area of vinyl chloride between 4 and 22%, that is, 40,000 and 200,000 ppm excluding the first few minutes of exposure.

➢ ***Definition of the irreversible effects thresholds***

♦ **Non-Carcinogenic Effects Thresholds**

The analysis of non-carcinogenic effects described in the literature emphasizes that the main toxic effect of vinyl chloride is localised in the central nervous system and is characterised by a narcotic effect. This narcotic effect induces depression of the central nervous system (by altering neurone cell communications) causing cerebral anoxia whose degree of intensity determines lethality. There is no means of assessing or quantifying the extent of these lesions

causing either irreversible effects or lethal effects. Moreover, in the case of early treatment (oxygen therapy) at the time of vinyl chloride poisoning, the exposed individuals show no disorders in the following days, nor in the long term. The current state of knowledge is therefore insufficient to be able to set non-carcinogenic irreversible effects thresholds.

### ♦ Carcinogenic Effects Thresholds

Vinyl chloride is classified as a carcinogen in the case of chronic exposure by different organisms (category 1 of the European Union and the IARC).

The toxicological experts of the consensus group have therefore considered the question of adopting the carcinogenic effect as an irreversible critical effect following a single exposure of short duration.

The experimental data relating to prove a carcinogenic effect under these exposure conditions are quite scarce. Only the works of Hehir (1981) and Tatraï (1981) have been identified in the literature.

The toxicological experts of the consensus group decided not to adopt these studies since the hepatic and pulmonary tumours described in the animals are isolated cases whose prevalence corresponds to the spontaneous rate for this kind of tumour in the species concerned. Moreover, they are specific to animals and have not been described in humans as a result of a single exposure to vinyl chloride. Only cases of hepatic angiosarcomas are known for chronic exposures in humans.

The group also pondered the relevance of extrapolating toxicological reference values (TRV) established for whole life exposures to short exposures.

Within the context of assessing health risks for a repeated exposure over a long period to a carcinogenic substance without a threshold (genotoxic) the concept of unit excess risk (ERU) is adopted. ERUs are estimated from epidemiological or experimental studies on animals.

For vinyl chloride, International organisations have published toxicological reference values for chronic exposures over a whole lifetime. In France, the circular of the Ministry of Ecology and Sustainable Development of 2nd August 2001 relating to classified installations using vinyl chloride monomer adopts that of the WHO guideline (2000), that is, an ERU of $10^{-6}$ $(\mu g/m^3)^{-1}$ for acceptance risk of $10^{-5}$. (transparent).

If a relationship is assumed where the product of the exposure concentration multiplied by the time of exposure is a constant, one can calculate a given acceptable Individual excess risk (for example $10^{-5}$) which corresponds to a wholelife (613200 hours) exposure concentration of 10 $\mu g/m^3$, the concentration corresponding to a one or eight hours exposure.

The concentrations thus obtained are listed in the following table (transparent)

| | Exposure time 1 hour | | Exposure time 8 hours | |
|---|---|---|---|---|
| ERI | $mg/m^3$ | ppm | $mg/m^3$ | ppm |
| $10^{-5}$ | 6,132 | 2,360 | 767 | 295 |

The values are only given as an example, since knowledge of cancer-triggering mechanisms is insufficient to confirm this extrapolation over several orders of magnitude of exposure concentration. The existing data rather lead to reject this approach, since the genotoxic properties of vinyl chloride are linked to its main metabolite (chloroethylene oxide) and not to vinyl chloride itself. The genotoxic action of this metabolite is expressed in the formation of DNA adducts. This kind of genic lesion is characterised by a low probability of tumour development.

Furthermore, examination of the toxicokinetics of this substance also shows that the formation of this carcinogenic metabolite is a saturable phenomenon for concentrations between 3000 and 7000 ppm (Withey, 1976).

Taking these factors into account, the toxicological experts of the consensus group finally concluded that the present state of knowledge precluded setting threshold values for irreversible carcinogenic effects associated with a single exposure.

**In conclusion** :

This is the point of view of the French "group de consensus" which has been validated within INERIS organisation.

It must be emphasised that French Acute toxicity thresholds are set :

- in a regulatory context to make prevention for land use planning.
- taking into account two acute thresholds whose definitions are exact to select critical studies and critical effects. For example : for lethality effects, the group examine lethality studies and no other.
- Regarding the uncertainty factors with a less conservative approach than that of the AEGL Committee but a protective approach for the general population.