

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Probit function technical support document

Date: 6 June 2017
Document id: 20170606-hydrogen chloride-INTERIM
Status: interim
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Commisioned by the RIVM

substance name	CAS number
Hydrogen chloride	7647-01-0

This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

This document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM). The contents of this document, including the probit function, has been approved by the Dutch Expert Panel on Probit Functions on scientific grounds. External parties have had the opportunity to comment on the derivation of the proposed probit function. The status of this document has now been raised to "interim", pending a decision on its formal implementation.

The decision on actual implementation depends on the results of a further consequence analysis.

Detailed information on the procedures for the derivation, evaluation and formalization of probit functions is available at <http://www.rivm.nl/>.

1 Technical support document Hydrogen chloride

3 1. Substance identification

4	CAS-number:	7647-01-0
5	IUPAC name:	Hydrogen Chloride
6	Synonyms:	hydrochloric acid, muriatic acid
7	Molecular formula:	H-Cl
8	Molecular weight:	36.47
9	Physical state:	gas (at 20°C and 101.3 kPa)
10	Boiling point:	-85°C (at 101.3 kPa)
11	Vapour pressure:	4300 kPa (at 20°C)
12	Saturated vapour conc:	gas (at 20°C)
13	Conversion factor:	1 mg/m ³ = 0.660 ppm (at 20°C and 101.3 kPa)
14		1 ppm = 1.52 mg/m ³ (at 20°C and 101.3 kPa)
15	Labelling:	H: 331-314

18 2. Mechanism of action and toxicological effects following acute exposure

20 **Acute effects:** The main target organs and tissues for inhalation exposure to HCl are
21 the cornea, conjunctiva, skin and respiratory tract. HCl dissolves in the mucous
22 membranes of the respiratory tract and eyes to form hydrochloric acid, a strong acid
23 that produces coagulative necrosis. The health endpoints are all related to the
24 irritative and corrosive properties of HCl. Symptoms of high exposure are laboured
25 breathing, secretions from nose, mouth and eyes and prostration.

26 Damage occurs in the respiratory system, particularly the upper respiratory tract
27 resulting in mucus secretion, upper airway and/or pulmonary oedema and
28 laryngospasm. The resulting hypoxemia will cause CNS and cardiovascular
29 (myocardial ischemia) effects. Lethality results when the respiratory damage proceeds
30 to inflammation, degeneration and necrosis of affected tissue, atelectasis,
31 emphysema and finally death (AHLS 2014, NRC 2004).

32 **Long-term effects:** Chronic exposure produces essentially the same type of health
33 effects. Reactive Airways Dysfunction Syndrome, an acquired asthma-like condition
34 has been described to develop after single exposure to a high concentration of HCl.
35 Symptoms occur within minutes to hours after the initial exposure and may persist as
36 non-specific bronchial hyperresponsiveness for months to years.

39 3. Human toxicity data

40 No informative reports on lethality in humans following acute inhalation exposure
41 were identified. Such reports are considered informative if both health effects as well
42 as the exposure have been documented in sufficient detail.

44 The following two studies of human exposure to HCl were identified.

45 In an experimental study 10 young adult asthmatic subjects were exposed to 2.7
46 mg/m³ for 45 minutes. This is the highest experimental exposure reported in
47 literature. No lethality or irreversible effects were reported (Stevens *et al* 1992, as
48 cited in NRC 2004).

49 An epidemiological study of occupational cancer mortality in groups with average
50 exposure up to 5.7 mg/m³ for durations up to >5 years did not report acute fatalities
51 (Siemiatycki 1991, as cited in NRC 2004).

52 In view of the exposure levels and reported health effects, these studies have not
53 been evaluated in more detail.

4. Animal acute toxicity data

During the literature search the following technical support documents and databases were consulted:

1. AEGL final TSD (2004), ERPG document and EU RAR and reference database for hydrogen chloride, covering references before and including 1995.
2. An additional search covering publications from 1980 onwards was performed in HSDB, MEDline/PubMed, Toxcenter, ECHA, IUCLID, RTECS, IRIS and ToxNet with the following search terms:
 - Substance name and synonyms
 - CAS number
 - lethal*
 - mortal*
 - fatal*
 - LC₅₀, LC
 - probit
3. Unpublished data were sought through networks of toxicological scientists.

Animal lethal toxicity data focused on acute exposure are described in Appendix 1. A total of 15 studies were identified -with 18 datasets for 4 species- with data on lethality following acute inhalation exposure. Four datasets were assigned status A for deriving the human probit function, 8 datasets were assigned status B1, no datasets were assigned status B2 and 6 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation¹

A total of 5 studies were identified in which sensory irritation was studied. In these studies the following RD₅₀ values were observed:

Table 1 Sensory irritation data for hydrogen chloride

Species/strain	RD ₅₀ (mg/m ³)	Exposure duration (min)	Author/year
Mouse	470 ^P	10	Barrow et al 1977
Swiss Mouse	520 ^{NS}	3	Terrill et al 1976
ChR-CD rat	1160 ^P	10	Gardner 1980
Rat	605 ^P	30	Arts et al 2000
Rat	608 ^{NS}	5-60	Lapin 1981

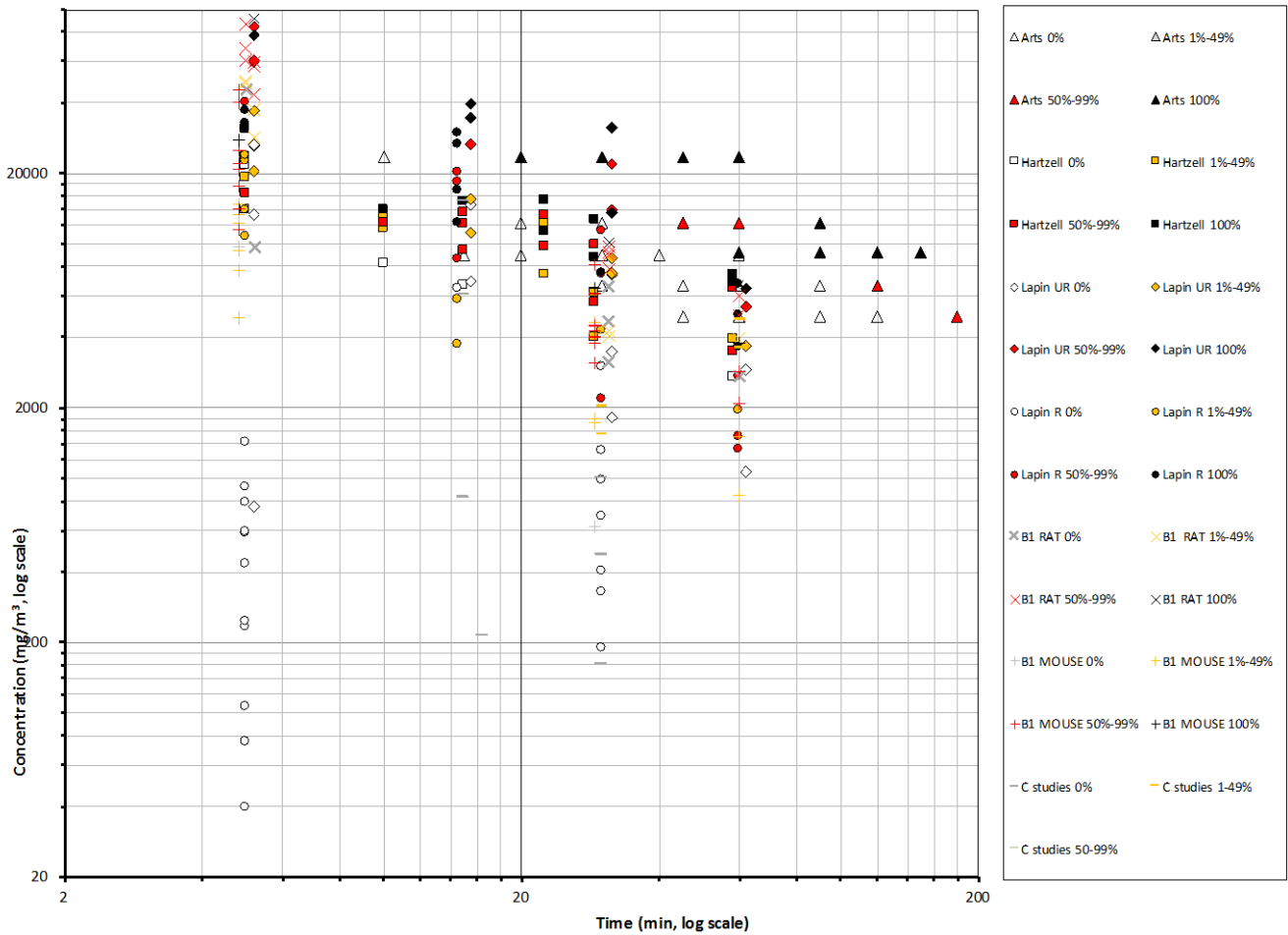
P: a plateau was reached, NS: not specified if a plateau in response was reached.

While in the rat the respiratory rate decreases during acute exposure to HCl (the RD₅₀ value appears to be around 600-1200 mg/m³), exposure of baboons to 787-885 mg/m³ resulted in an increased respiratory rate and minute volume, without a change in tidal volume (Kaplan *et al* 1993).

¹ Delete table if no applicable studies are identified. In that case, include text: No studies on sensory irritation were found.

1 **5. Probit functions from individual studies**

2 All available acute lethality data on hydrogen chloride are provided in Figure 1.



3 **Figure 1** All available acute lethality data for hydrogen chloride

4
5 All A and B1 studies were initially selected for derivation of the animal probit function
6 for hydrogen chloride. The data that were selected for primary analysis of the animal
7 probit function are presented in Table 2 and Figure 3.

8
9 To enable intra-species pooling, LC₅₀-values of B1-studies were scaled using the
10 average rat n-value of 1.367 for HCl with the following formula:

$$LC_{50,c} = LC_{50,test} \left(\frac{t_{test}}{t_c} \right)^{(1/n)}$$

11
12
13 With LC_{50,c} = scaled LC₅₀ value for common exposure duration t_c
14 LC_{50,test} = observed LC₅₀ value for tested exposure duration
15 t_c = common exposure duration for intra-species pooling
16 t_{test} = tested exposure duration
17
18

1 **Table 2** Data selected for initial analysis of the animal probit function of Hydrogen
2 Chloride.

Study ID	Species	Probit (C in mg/m ³ , t in min)	LC ₅₀ at tested exposure duration (mg/m ³) 95% C.I.	LC ₅₀ , 30 minutes (mg/m ³) 95% C.I. (<i>underline italic for scaled values</i>)	n-value 95% C.I.
A.1	Rat	-73.9 + 6.67×lnC + 4.19×Int		15580 (13350 - 18770)	1.59 (1.26–1.92)
A.2	Rat	-21.6 + 2.39×lnC + 1.64×Int		6671 (5527 - 7730)	1.46 (1.12-1.79)
A.3	Rat*	-12.6 + 1.46×lnC + 1.39×Int		6791 (5718 - 8006)	1.05 (0.88-1.21)
A3	Rat**	-14.6 + 1.62×lnC + 1.78×Int		4322 (3613 - 5064)	1.03 (0.87-1.19)
A3	Rat***	-31.8 + 2.85×lnC + 3.13×Int		9690 (8887 - 10550)	1.10 (0.97-1.22)
B1.1	Rat	30 min LC ₅₀		7684 (6906 - 8496)	N/A
B1.2	Mouse	30 min LC ₅₀		3616 (3093 - 4081)	N/A
B1.3	Rat	60 min LC ₅₀	5502 - 60 min (4656 - 7691)	<u>9136</u>	N/A
B1.4	Rat	60 min LC ₅₀	4748 - 60 min (4174 - 5246)	<u>7884</u>	N/A
B1.5	Mouse	60 min LC ₅₀	1648 - 60 min (1219-2138)	<u>2796</u>	N/A
B1.6	Rat	5 min LC ₅₀	62220 - 5 min (56770-69150)	<u>16776</u>	N/A

3 * all data: pooled data from restrained and unrestrained animals

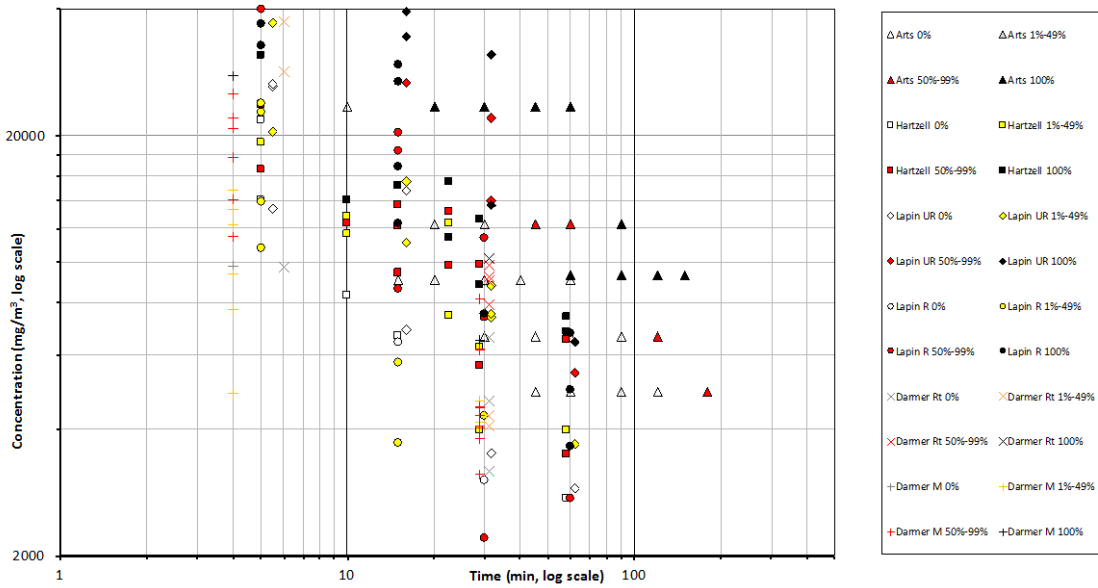
4 ** restrained animals

5 *** unrestrained animals

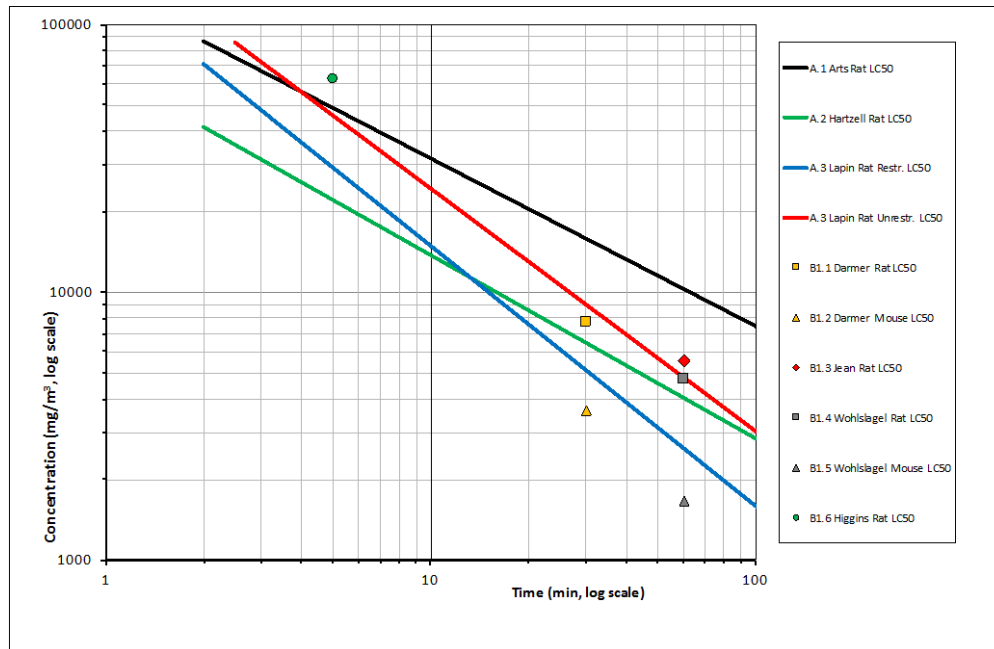
6

7

1 The data of the 3 A studies and 4 B1 studies are presented graphically below.



2 **Figure 2** Data selected for the initial analysis for the derivation of the animal probit
 3 function of hydrogen chloride (all A studies and B1 studies).
 4
 5



6
 7 **Figure 3** LC₅₀ values of A and B1 datasets for hydrogen chloride, over time where
 8 available.
 9

10 Based on visual inspection and the criteria outlined in the guideline the data from all A
 11 studies and from B1 studies in rats and mice with 30- and 60-minute data were
 12 selected for the final dataset for the derivation of the animal probit function. Mice
 13 appear to be substantially more susceptible to the acute effects of HCl exposure.
 14 Despite the unexplained difference in response to restraining, all data from Lapin
 15 (1981) are used for the final analysis. The final data eligible for calculating the animal
 16 probit function contains 11 datasets from 7 studies and includes data from 2 animal
 17 species. The 5-minute rat data from study B1.6 serve as supportive evidence.

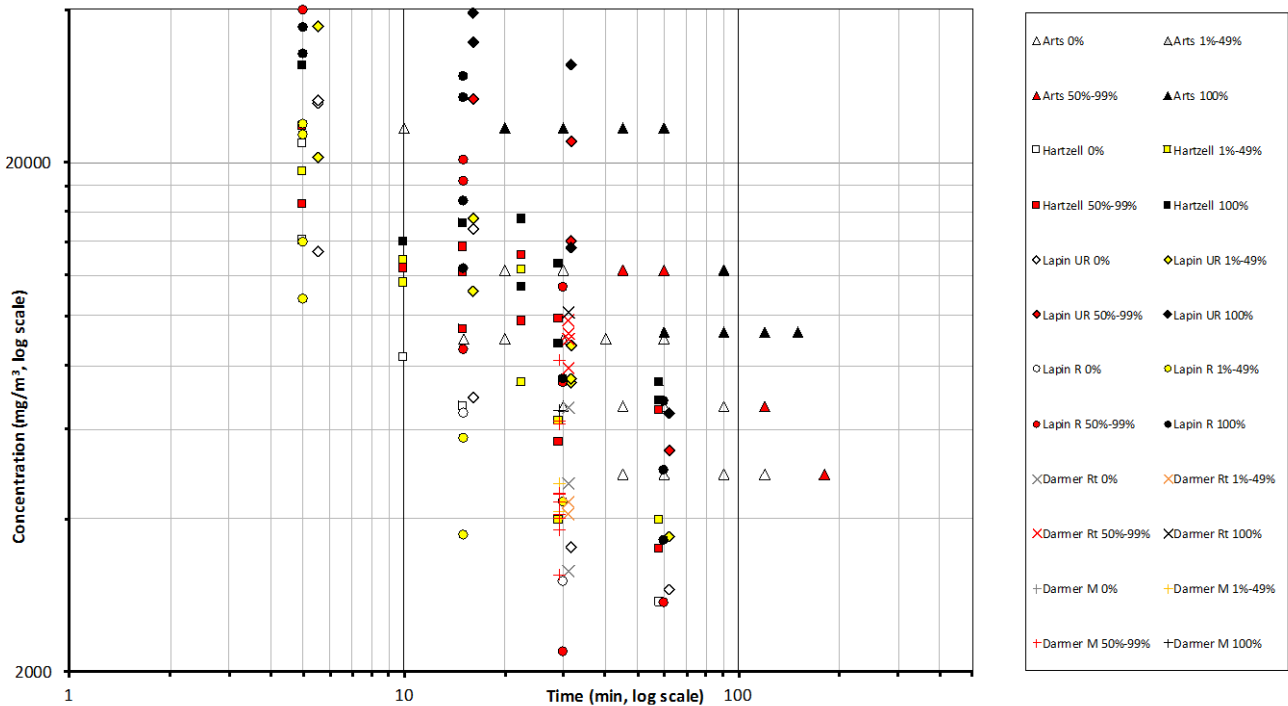
1 **Table 3** Data selected for the derivation of the animal probit function of hydrogen
 2 chloride.

Study ID	Species	Probit (C in mg/m ³ , t in min)	LC ₅₀ at tested exposure duration (mg/m ³) 95% C.I.	LC ₅₀ , 30 minutes (mg/m ³) 95% C.I. (<i>underline italic for scaled values</i>)	n-value 95% C.I.
A.1	Rat	-73.9 + 6.67×lnC + 4.19×Int		15580 (13350 - 18770)	1.59 (1.26–1.92)
A.2	Rat	-21.6 + 2.39×lnC + 1.64×Int		6671 (5527 - 7730)	1.46 (1.12-1.79)
A.3	Rat*	-12.6 + 1.46×lnC + 1.39×Int		6791 (5718 - 8006)	1.05 (0.88-1.21)
B1.1	Rat	30 min LC ₅₀		7684 (6906 - 8496)	N/A
B1.2	Mouse	30 min LC ₅₀		3616 (3093 - 4081)	N/A
B1.3	Rat	60 min LC ₅₀	5502 - 60 min (4656 - 7691)	<u>9136</u>	N/A
B1.4	Rat	60 min LC ₅₀	4748 - 60 min (4174 - 5246)	<u>7884</u>	N/A
B1.5	Mouse	60 min LC ₅₀	1648 - 60 min (1219-2138)	<u>2796</u>	N/A

3 * all data: pooled data from restrained and unrestrained animals

4

5 The data of the selected datasets are presented graphically in Figure 4.



6 **Figure 4** Final data selected for derivation of the animal probit function of hydrogen
 7 chloride.

8

6. Derivation of the human probit function

To derive the human probit function the results from the studies by Arts (2000), Hartzell (1987), Lapin (1981), Darmer (1974), Jean (2006), Wohlschlager (1976) and Higgins (1972) have been used to derive a point of departure. These studies qualified for the derivation of a probit function based on the criteria outlined in the methodology (Ruijten *et al* 2015). The results of study B1.3 (Jean) were used with a weight of 0.5 because only nominal concentrations were reported. The 5-minute rat data from study B1.6 (Higgins) serve as supportive evidence.

First, the arithmetic mean species-specific (rat) n-value was calculated to be 1.367.

Second, the LC₅₀-values of all A- and B1-studies were calculated for a common exposure duration of 30 minutes. To enable this intra-species pooling, LC₅₀-values of B1-studies were scaled using the rat n-value of 1.367 for HCl with the following formula:

$$LC_{50,c} = LC_{50,test} \left(\frac{t_{test}}{t_c} \right)^{(1/n)}$$

With LC_{50,c} = scaled LC₅₀ value for common exposure duration t_c
 LC_{50,test} = observed LC₅₀ value for tested exposure duration
 t_c = common exposure duration for intra-species pooling
 t_{test} = tested exposure duration

Next, the weighted species-specific geometric mean LC₅₀-values were calculated from all available (scaled) LC₅₀ values. The weighted species-specific geometric mean LC₅₀ value is 8498 mg/m³ for rats and 3180 mg/m³ for mice. Finally, an unweighted geometric mean overall LC₅₀-value was calculated.

The formula for the pooling of the selected weighted and scaled LC₅₀-values is as follows:

$$\overline{LC}_{50} = \left[\prod_{j=1}^s \exp \left(\frac{\sum_{i=1}^m w_i \times \ln(LC_{50,i})}{\sum_{i=1}^m w_i} \right) \right]^{(1/s)}$$

With \overline{LC}_{50} = geometric mean LC₅₀-value across species
 LC_{50,i} = LC₅₀-value of study i
 w = weight factor for study usefulness, default = 1
 m = number of observations on LC₅₀-values within a species (i=1...m).
 s = number of species for which LC₅₀-values are pooled (j= 1...s).

The 30-minute weighted geometric mean LC₅₀ value was 5198 mg/m³, the arithmetic mean n-value was 1.367.

In addition to the rodent data, the expert panel made the following observations:

- 3/3 baboons survived a 15-minute exposure to approximately 15000 mg/m³ HCl (Kaplan *et al* 1988), while HCl exposure to 15000 mg/m³ (Hartzell *et al*) and 12000 mg/m³ (Lapin) for 15 minutes is fatal to 6/6 rats.
- The respiratory response of baboons (and therefore maybe in man) is clearly different from that in rats (Kaplan *et al* 1988, 1993).

Based on the primate data from Kaplan *et al* (1988, 1993) it was argued that the derivation of a probit function from rat and mouse data may overestimate the acute lethality of HCl in non-human primates and therefore most likely also in humans, assuming that baboons are a better model for lethality in humans than rats.

1 The human equivalent LC₅₀ was calculated by applying the following assessment
2 factors:

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	1	Based on the available data on survival in baboons, an assessment factor of 1 was judged to be appropriate for HCl.
Nominal concentration	1	All reported concentrations are analytical.
Adequacy of database:	1	HCl has a strong database with 3 A studies and 6 B1 studies.

4
5 The estimated human equivalent 30-minute LC₅₀ value is $5198 / 1 = \mathbf{5198 \text{ mg/m}^3}$.

6
7 The experimentally determined weighted average n-value was **1.367** (studies A1, A2
8 and A3). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the
9 b-value can be calculated as $2 / n = \mathbf{1.463}$.

10
11 The human probit function is then calculated on the human equivalent 30 min LC₅₀
12 using the above parameters to solve the following equation to obtain the a-value (the
13 intercept): $5 = a + 1.463 \times \ln(5198^{1.367} \times 30)$ resulting in the a-value of **-17.09**.

14
15 **Pr = -17.1 + 1.46 × ln (C^{1.37} × t) with C in mg/m³ and t in min.**

16
17 The derived human probit function has a scientifically sound basis. The probit function
18 is based on 6 studies on HCl (6 rat and 2 mouse datasets) with A and B1 quality, with
19 exposure durations ranging from 5 to 180 minutes and exposure concentrations
20 ranging from 40 to 78.000 mg/m³.

21
22 The human 60 min LC_{0.1} (Pr = 1.91) calculated with this probit equation is 676 mg/m³
23 and the calculated human 60 min LC₁ (Pr = 2.67) is 988 mg/m³.

Estimated level	30 min (mg/m ³)	60 min (mg/m ³)
0.1% lethality, this probit	1120	676
1% lethality, this probit	1638	988
AEGL-3 (2004, final)	210	100
ERPG-3 (2015)		228
LBW (2015)	240	150

25
26 Compared with equivalent (inter)national guideline levels as presented in the table
27 above, the lethal levels derived with this probit function are higher. AEGL and ERPG
28 values have been set with higher assessment factors to allow a wider margin of safety
29 for susceptible individuals. However, despite these higher values, the baboon data
30 suggest that this probit function leaves some margin of safety: the 15-minute LC₀₁
31 value based on the proposed probit function is 2717 mg/m³, where 3/3 baboons
32 survived a 15-min exposure to 15000 mg/m³.

Appendix 1 Animal experimental research

Study ID: A.1

Author, year: Arts et al 2000

Substance: Hydrogen Chloride
 Species, strain, sex: Male and female rats, unspecified strain
 Number/sex/conc. group: 1 / C×T combination / sex, total number of animals 58
 Age and weight: unspecified
 Observation period: 14 days

Evaluation of study quality

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to guideline(s)	<i>Equivalent to OECD 403 (10 animals per concentration); In this study 1 animal/sex/C×T combination was used</i>
Stability of test compound in test atmosphere	<i>Some evidence of aerosol formation at 12,300 and 23,400 mg/m³ concentrations.</i>
Use of vehicle (other than air)	<i>Dry air (relative humidity 1%)</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Head/nose only</i>
Type of restrainer	<i>Batelle tube, adequate restrainer</i>
Pressure distribution.	<i>Positive pressure at the nose of the animals (central cylinder), negative pressure in surrounding hood</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Empty animal location used as sampling point; based on air flow (see below,) homogeneity expected to be present</i>
Number of air changes per hour	<i>100 l/min (cylinder volume 50 l) for 10 rats, i.e. air flow is sufficient</i>
Equilibration time (t95)	<i>1.5 minutes</i>
Start of exposure relative to equilibration	<i>After complete equilibration</i>
Actual concentration measurement	<i>Acid/base titration based on colour change of titration fluid and amount of air passed through. This method may have produced biased concentration estimates due to interference of CO₂ exhaled by the animals.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>N/A</i>
Assessment of Reliability	A <i>Well performed study</i>

1 **Results**

2

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			Male	Female
Rat	4890	45/60/90/120/180	0/0/0/0/1	0/0/0/0/0
Rat	6620	30/45/60/90/120	0/0/0/0/1	0/0/0/0/0
Rat	9020	15/20/30/40/60	0/0/0/0/0	0/0/0/0/0
Rat	9250	60/90/120/150	1/1/1/1	1/1/1/1
Rat	12300	20/30/45/60/90	0/0/1/0/1	0/0/0/1/1
Rat	23400	10/20/30/45/60	0/1/1/1/1	0/1/1/1/1

3
4
5 **Probit function**

6 The probit function and associated LC-values have been calculated using the
7 DoseResp program (Wil ten Berge, 2015) as

8 $Pr = a + b \times \ln C + c \times \ln t + d \times S$

9 with C for concentration in mg/m³, t for time in minutes and S for sex (0 = female, 1
10 = male).

11

Probit function	Species	a	b	C	d	n-value
Sex as covariate	Rat	-73.9	6.67	4.19	0.53	1.59 (1.26 - 1.92)
Sexes combined	Rat	-73.3	6.64	4.17		1.59 (1.26 - 1.93)

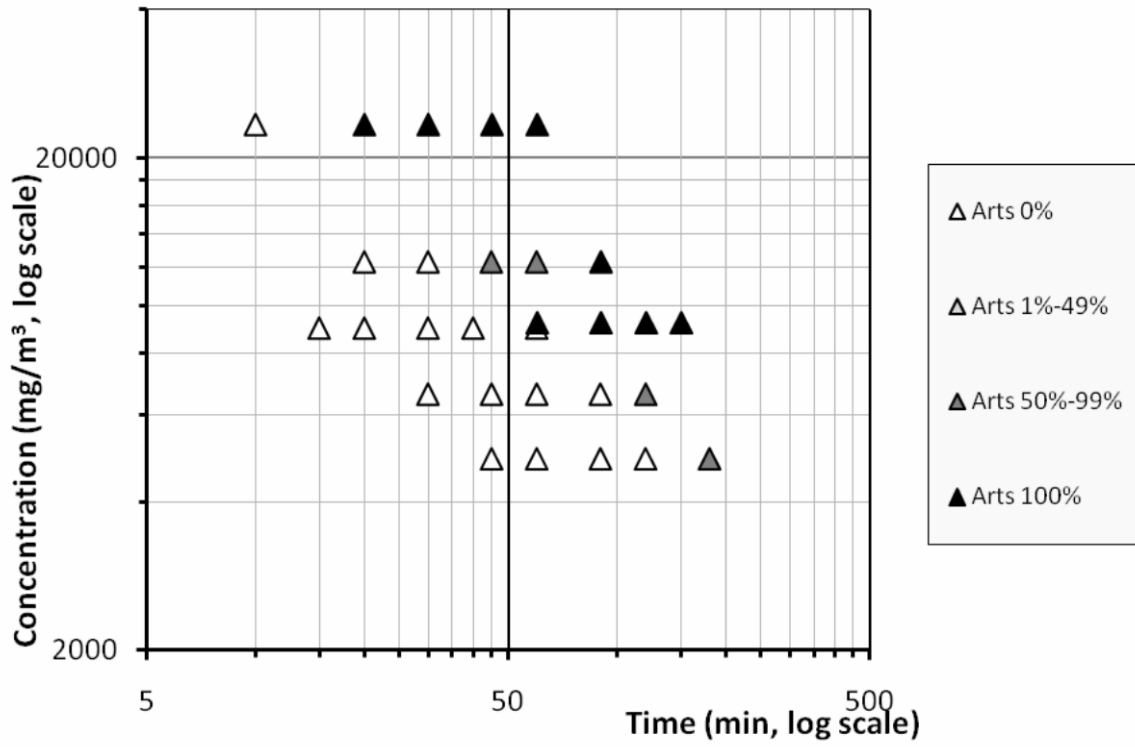
12
13 The LC₅₀ values for both sexes did not differ by more than a factor of 2, nor did
14 analysis with sex as covariate give any indication that sex differences exist. This does
15 not support the proposition that sex differences exist in the lethal response. For this
16 reason the data from both sexes were pooled and analysed to derive the animal
17 probit function.

18

Duration (min.)	LC ₅₀ (mg/m ³) 95%-CI Male	LC ₅₀ (mg/m ³) 95%-CI Female	LC ₅₀ (mg/m ³) 95%-CI Sexes combined
10	29930 (21780 - 42990)	32420 (23560 - 47120)	31070 (22970 - 44100)
30	15000 (12460 - 18570)	16250 (13480 - 20360)	15580 (13350 - 18770)
60	9702 (8376 - 11440)	10510 (9066 - 12540)	10070 (9096 - 11420)

19
20
21 The results for males and females were derived from the analysis with sex as
22 covariate. If the male and female datasets were analyzed separately, the outcome
23 was slightly different. The 30-min LC₅₀ value (mg/m³) for males was 15,930 (11,750 -
24 24,810) and for females 15,130 (12,030 - 24,860).

25
26
27 A graphical overview of the data is presented below. Each concentration-time
28 combination (with 1 male and 1 female animal) represents one point in the plot.
29



1
2
3

1 **Study ID: A.2**2 **Author, year: Hartzell et al 1985**

3
4 Substance: Hydrogen Chloride
5 Species, strain, sex: Rat, male Sprague-Dawley
6 Number/sex/conc. group: 6-8 / group (all male)
7 Age and weight: adult, weight unspecified
8 Observation period: 14 days
9

10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to guideline(s)	<i>No mention of guideline OECD 403</i>
Stability of test compound in test atmosphere	<i>Aerosol formation</i>
Use of vehicle (other than air)	<i>Air</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Head-only (in restrainer tubes), placed in small clean air space during chamber equilibration</i>
Type of restrainer	<i>'tubular restrainers', not otherwise specified</i>
Pressure distribution.	<i>Not specified</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified</i>
Number of air changes per hour	<i>Not specified</i>
Equilibration time (t95)	<i>Unable to calculate because the airflow was not specified.</i>
Start of exposure relative to equilibration	<i>As stated by the authors: <u>after complete equilibration a hinged box was opened and the animals exposed to the verified concentration.</u></i>
Actual concentration measurement	<i>Batch sampling with soda lime near breathing zone to determine analytical concentration. Intermittent sampling of small aliquots analysed with Ion Specific Electrode Continuous sampling (conductivity detector) to maintain stable HCl level during the test.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>Not available</i>
Assessment of Reliability	A

11
12 For the probit calculations it is assumed that the exposure of the animals is almost
13 instantaneously to the measured concentration, even though some dilution may have
14 been present.

15
16 The figure below shows how the restrained animals were exposed. The hinged box
17 used by Hartzell et al resembles that used by Lapin (study A3). The authors claim
18 that animals receive a true 'square wave' exposure pattern without a (significant)
19 equilibration period.

1 For the probit calculations it is assumed that the
 2 exposure of the animals is almost
 3 instantaneously to the measured concentration,
 4 even though some dilution may have been
 5 present.

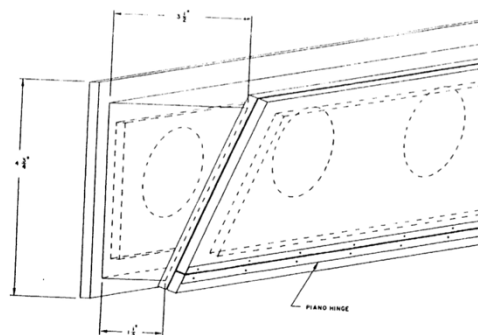


Figure 2. Diagram of animal isolation system.

11 **Results**

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			Exposed	Responded
rat	13984	5	6	0
rat	16530	5	6	3
rat	19128	5	6	2
rat	21747	5	6	0
rat	23498	5	6	3
rat	30856	5	6	6
rat	8275	10	6	0
rat	11596	10	6	1
rat	12333	10	8	5
rat	12806	10	8	1
rat	13938	10	6	6
rat	6627	15	6	0
rat	9380	15	6	3
rat	12130	15	6	4
rat	13619	15	6	4
rat	15185	15	6	6
rat	7393	22.5	6	2
rat	9749	22.5	6	4
rat	11380	22.5	6	6
rat	12317	22.5	6	2
rat	13142	22.5	8	4
rat	15408	22.5	6	6
rat	3967	30	6	2
rat	5644	30	6	4
rat	6217	30	6	1
rat	8780	30	8	8
rat	9834	30	6	4
rat	12586	30	6	6

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			Exposed	Responded
rat	2725	60	6	0
rat	3467	60	6	3
rat	3952	60	6	1
rat	6501	60	8	7
rat	6779	60	6	6
rat	7378	60	6	6

1

2 **Probit function**3 The probit function and associated LC-values have been calculated using the
4 DoseResp program (Wil ten Berge, 2015) as

5
$$Pr = a + b \times \ln C + c \times \ln t$$

6 with C for concentration in mg/m³ and t for time in minutes.

7

8 To test the sensitivity of the model outcome for in- or exclusion of the 5-minute data
9 the models were developed both including and excluding the 5-minute data.

10

<i>Probit function</i>	<i>Species</i>	<i>a</i>	<i>b</i>	<i>c</i>	<i>n-value</i>
Including 5 min exposure	<i>Rat</i>	-21.58	2.39	1.64	1.46 (1.12 - 1.79)
Excluding 5 min exposure	<i>Rat</i>	-20.68	2.31	1.56	1.48 (0.97 - 1.99)

11

12 The analysis with and without the 5-min exposure essentially gave the same result,
13 and are both presented below. All further analyses will be based on the model
14 including the 5-minute data.

15

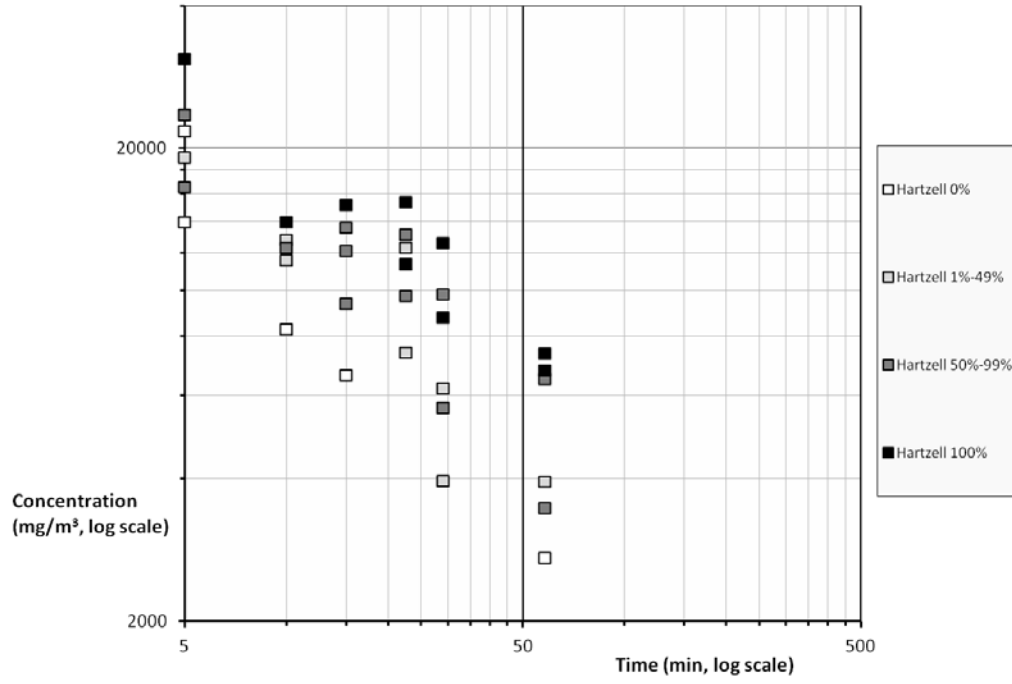
<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%-C.I. With 5 min data</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Without 5 min data</i>
10	14190 (12170 - 16730)	13990 (10870 - 18320)
30	6671 (5527 - 7730)	6654 (5390 - 7770)
60	4144 (3081 - 5176)	4163 (2891 - 5415)

16

17

18 A graphical overview of the data is presented below. Each concentration-time
19 combination (with 6-8 animals) represents one point in the plot.

20



1
2
3

1 **Study ID: A.3**2
3 **Author, year: Lapin 1981**

4 Substance: Hydrogen Chloride

5 Species, strain, sex: Rat, male Crl:CD

6 Number/sex/conc. group: 6 (restrained), 10 (unrestrained) group

7 Age and weight: adult, weight 250 ± 25 grams

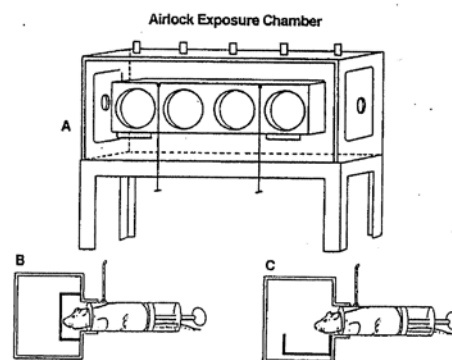
8 Observation period: 14 days

9
10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to guideline(s)	<i>No mention of guideline OECD 403. Light/dark cycle, temperature, humidity and food/water provision consistent with OECD guideline 403 criteria.</i>
Stability of test compound in test atmosphere	<i>Aerosol formation not reported.</i>
Use of vehicle (other than air)	<i>Air.</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Restrained: Head only. Rats were restrained in whole body holders inside the chamber (175 l) used (in some cases simultaneously) for unrestrained animals. By using a switch a hinged box was swung down to start an exposure (see figure below). Unrestrained: whole body, 10 animals in 175 l chamber.</i>
Type of restrainer	<i>'whole body holders', not otherwise specified</i>
Pressure distribution.	<i>Not specified.</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>'The test gas chamber atmospheres were generated with continuous flow-through generation. Gas concentrations were generated by dilution of commercial bottled gas.'</i>
Number of air changes per hour	<i>Not specified.</i>
Equilibration time (t95)	<i>unable to calculate; no air changes per hour provided.</i>
Start of exposure relative to equilibration	<i>'...once a satisfactory steady state chamber concentration of the test material was obtained.'</i>
Actual concentration measurement	<i>Intermittent sampling ('at frequent intervals') of 47 ml aliquots in a syringe with 3 ml sodium acetate. Analysis with a Cl⁻ Specific Ion Electrode.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>Not specified, formation of aerosol uncertain.</i>
Assessment of Reliability	A <i>Data were suitable to derive a probit function. Multiple concentration levels and durations were tested, resulting in a good concentration response relation with mortality of 0-100%.</i>

1 The figure shows how the restrained animals
 2 were exposed. Figures A and B show respectively
 3 a closed and opened hinged box. The authors
 4 claim that animals receive a true 'square wave'
 5 exposure pattern without a (significant)
 6 equilibration period.

7
 8 For the probit calculations it is assumed that the
 9 exposure of the animals is almost
 10 instantaneously to the measured concentration,
 11 even though some dilution may have been
 12 present.



A) front view, B) end view, atmosphere pre-equilibrated while rats breathe fresh air, and C) airlock dropped for instantaneous exposure

15 Results

Species	Concentration (mg/m ³)	Exposure duration(min)	Restrained	Exposed	Responded
Rat	39	5	Yes	6	0
Rat	76	5	Yes	6	0
Rat	106	5	Yes	6	0
Rat	234	5	Yes	6	0
Rat	244	5	Yes	6	0
Rat	432	5	Yes	6	0
Rat	581	5	Yes	6	0
Rat	595	5	Yes	6	0
Rat	792	5	Yes	6	0
Rat	916	5	Yes	6	0
Rat	916	5	Yes	6	0
Rat	1423	5	Yes	6	0
Rat	10765	5	Yes	6	1
Rat	13922	5	Yes	6	2
Rat	22645	5	Yes	6	2
Rat	23759	5	Yes	6	2
Rat	32668	5	Yes	6	6
Rat	36752	5	Yes	6	6
Rat	39908	5	Yes	6	3
Rat	3703	15	Yes	6	1
Rat	5754	15	Yes	5	1
Rat	6435	15	Yes	6	0
Rat	8585	15	Yes	6	3
Rat	12344	15	Yes	6	6
Rat	16798	15	Yes	6	6

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Species	Concentration (mg/m ³)	Exposure duration(min)	Restrained	Exposed	Responded
Rat	18376	15	Yes	6	5
Rat	20268	15	Yes	6	5
Rat	26729	15	Yes	5	5
Rat	29513	15	Yes	5	5
Rat	188	30	Yes	6	0
Rat	329	30	Yes	6	0
Rat	405	30	Yes	5	0
Rat	687	30	Yes	6	0
Rat	982	30	Yes	6	0
Rat	1305	30	Yes	6	0
Rat	2191	30	Yes	4	2
Rat	3007	30	Yes	6	0
Rat	4301	30	Yes	6	1
Rat	7371	30	Yes	6	4
Rat	7531	30	Yes	6	6
Rat	11349	30	Yes	6	4
Rat	1330	60	Yes	4	2
Rat	1505	60	Yes	6	3
Rat	1952	60	Yes	6	1
Rat	2735	60	Yes	6	4
Rat	3621	60	Yes	6	6
Rat	4968	60	Yes	6	6
Rat	6768	60	Yes	6	6
Rat	762	5	No	10	0
Rat	13364	5	No	10	0
Rat	20418	5	No	10	1
Rat	26172	5	No	10	0
Rat	26542	5	No	10	0
Rat	37122	5	No	10	3
Rat	59396	5	No	10	9
Rat	60881	5	No	10	7
Rat	77957	5	No	10	10
Rat	84145	5	No	10	9
Rat	6898	15	No	10	0
Rat	11137	15	No	10	1
Rat	14775	15	No	10	0

Species	Concentration (mg/m ³)	Exposure duration(min)	Restrained	Exposed	Responded
Rat	15516	15	No	10	3
Rat	26635	15	No	10	8
Rat	34431	15	No	10	10
Rat	39443	15	No	10	10
Rat	39443	15	No	10	9
Rat	1834	30	No	10	0
Rat	3500	30	No	10	0
Rat	7371	30	No	10	3
Rat	7531	30	No	10	4
Rat	8750	30	No	10	1
Rat	13629	30	No	10	10
Rat	14001	30	No	10	7
Rat	22008	30	No	10	9
Rat	31183	30	No	10	10
Rat	1071	60	No	10	0
Rat	2893	60	No	10	0
Rat	3673	60	No	10	2
Rat	5439	60	No	10	8
Rat	6443	60	No	10	10

1
2 **Probit function**

3 The probit function and associated LC-values have been calculated using the
4 DoseResp program (Wil ten Berge, 2015) as

5 $Pr = a + b \times \ln C + c \times \ln t + d \times R$

6 Where C is concentration in mg/m³, t is exposure duration in minutes and R is a
7 dummy variable for restraintment.

8
9 First, the data were analysed for restrained and unrestrained animals separately.
10 Subsequently the data were analysed with both restrained and unrestrained animals,
11 with a dummy variable to account for restraintment.

12
13 To assess the influence of including the 5-min data and the use of restraintment, the
14 calculations were performed:

- 15 • with and without the 5-min data.
16 • for restrained and unrestrained animals separately.
17 • all animals in the model, with and without a dummy variable to account for
18 restraintment.
19

<i>Probit function</i>	<i>Species</i>	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>n-value</i>
Only restrained animals, INCL 5 min data	<i>Rat</i>	-13.30	1.55	1.50		1.03 (0.87 – 1.19)
Only restrained	<i>Rat</i>	-14.58	1.62	1.78		0.91 (0.69 – 1.13)

animals, EXCL 5 min data						
Only unrestrained animals, INCL 5 min data	<i>Rat</i>	-28.00	2.69	2.46		1.10 (0.97 – 1.22)
Only unrestrained animals, EXCL 5 min data	<i>Rat</i>	-31.83	2.85	3.13		0.91 (0.79 – 1.04)
All animals, INCL 5 min data, dummy	<i>Rat</i>	-20.49	2.07	1.93	1.55	1.07 (0.97 – 1.18)
All animals, EXCL 5 min data, dummy	<i>Rat</i>	-22.37	2.12	2.32	1.64	0.91 (0.75 – 1.08)
All animals, INCL 5 min data	<i>Rat</i>	-12.58	1.46	1.39		1.05 (0.88 – 1.21)

All LC₅₀ values calculated with the probit model are presented below. For comparison the LC₅₀ values as calculated by Lapin are also presented (calculated per exposure duration).

1. Restrained animals only

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%-C.I. With 5 min data</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Without 5 min data</i>	<i>LC₅₀ (mg/m³) Lapin</i>
10	12300 (10310 - 14510)	14450 (10220 - 20030)	**
30	4228 (3544 - 4962)	4322 (3613 - 5064)	5541
60	2155 (1677 - 2717)	2018 (1520 - 2621)	1837

2. Unrestrained animals only

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%-C.I. With 5 min data</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Without 5 min data</i>	<i>LC₅₀ (mg/m³) Lapin</i>
10	25860 (22990 - 29000)	32300 (26700 - 38880)	**
30	9493 (8466 - 10660)	9690 (8887 - 10550)	9750
60	5045 (4278 - 5872)	4533 (3929 - 5236)	4442

** Lapin only calculated LC₅₀ values for the tested exposure durations.

3. Restrained / unrestrained animals animals in one analysis incl. 5 min data

<i>Duration minutes</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Restrained animals</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Unrestrained animals</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Combined animals</i>
10	12300 (10510 - 14310)	26050 (23090 - 29380)	19430 (16470 – 22890)
30	4415 (3776 - 5133)	9352 (8268 - 10570)	6791 (5718 – 8006)
60	2313 (1915 - 2779)	4900 (4159 - 5769)	3499 (2726 – 4441)

Results for restrained/unrestrained animals in results table 3 taken from the combined analysis, by applying the parameter estimate of the dummy variable. Combined animals are numbers from an analysis without the dummy variable.

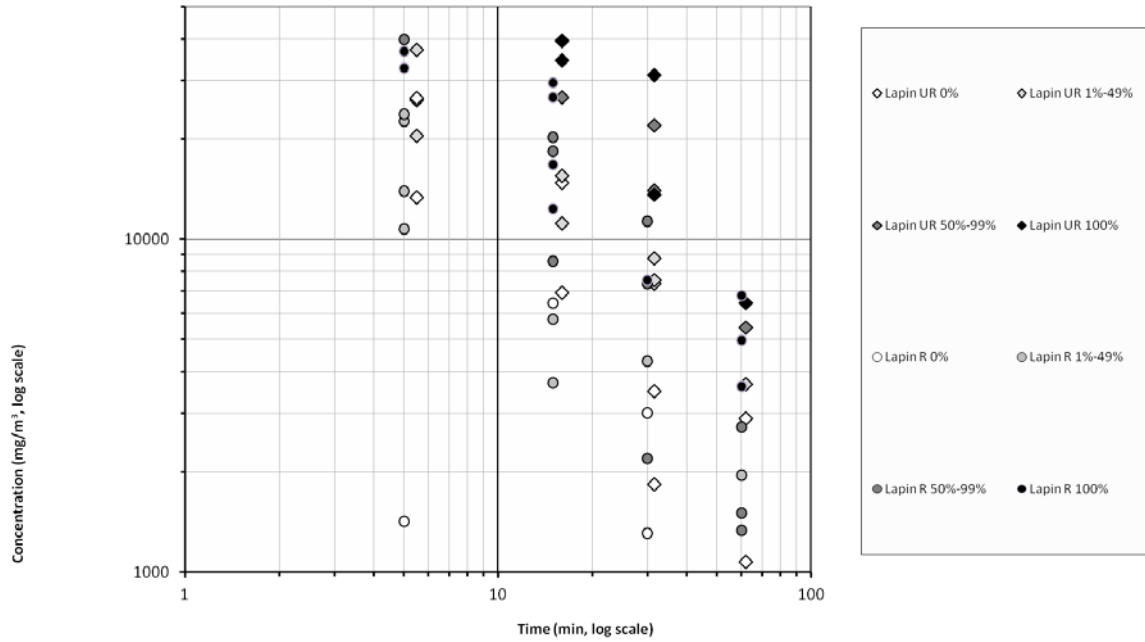
The calculated LC₅₀ values were systematically higher (lower toxicity) in unrestrained vs restrained animals by a factor 2.2-2.5. Stress or inability to avoid exposure in

1 restrained animals may have contributed, although there is no definitive explanation
2 for the difference.

3

4 A graphical overview of the data is presented below. Each concentration-time
5 combination (with 4-10 male rats) represents one point in the plot.

6



7

8

9

10

1 **Study ID: B1.1**3 **Author, year: Darmer 1974**

4 Substance: Hydrogen Chloride
 5 Species, strain, sex: Rat, CFE (Sprague-Dawley derived), sex unspecified
 6 Number/sex/conc. group: 10/concentration/time
 7 Age and weight: 250-300 grams, unspecified age (adult as judged from
 8 weight)
 9 Observation period: 7 days

11 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time; many details (housing, lighting, food, water, etc) not specified</i>
Stability of test compound in test atmosphere	<i>Not specified. Exposure to gas in pre-dried air (for gas exposures), OR gas introduced in nearly saturated water droplet mist (for aerosol exposures).</i>
Use of vehicle (other than air)	<i>Air</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body, animals introduced in chamber with little air loss after chamber concentration equilibrated</i>
Type of restrainer	<i>No restrainer used – whole body</i>
Pressure distribution.	<i>No information on pressure distribution; reference to publication that mentions 0.05 cm negative water pressure in the chamber</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified; air sampling appears to take place in animal breathing zone.</i>
Number of air changes per hour	<i>Air flow = 10cfm = 283 l/min = 17 m³/h, chamber volume is approx 2 m³, air exchange rate = 8.5/h</i>
Equilibration time (t95)	<i>3 × (2000 l / 283 l/min) = 21 min.</i>
Start of exposure relative to equilibration	<i>Animals were introduced into the chamber by means of sliding cage 'drawers' in the wall of the chamber</i>
Actual concentration measurement	<i>Continuous during exposure with specific chloride ion electrode (in breathing zone)</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No gravimetric assessment of droplet size, but optical method (semi-quantitative). Estimated diameter < 2 µm (water droplet size = aerodynamic Diameter, no droplets >5 µm observed)</i>
Assessment of Reliability	B1.1 This study received B status because only 2 exposure durations were studied and aerosol exposure was not well quantified. Sufficient other A-studies available.

1 **Results**

2

Species	Concentration (mg/m ³)	Exposure duration (min)	Gas or aerosol	Lethality	
				Exposed	Lethal
Rat	45600	5	Gas	10	0
Rat	49028	5	Gas	10	1
Rat	60572	5	Gas	10	6
Rat	68704	5	Gas	10	7
Rat	87081	5	Gas	10	9
Rat	3159	30	Gas	10	0
Rat	4071	30	Gas	10	1
Rat	4668	30	Gas	10	0
Rat	7874	30	Gas	10	5
Rat	9223	30	Gas	10	8
Rat	10155	30	Gas	10	10
Species	Concentration (mg/l)	Exposure duration (min)	Gas or aerosol	Lethality	
				Exposed	Lethal
Rat	9.7	5	Aerosol	10	0
Rat	28.4	5	Aerosol	10	1
Rat	37.3	5	Aerosol	10	3
Rat	43.6	5	Aerosol	10	6
Rat	57.0	5	Aerosol	10	6
Rat	60.1	5	Aerosol	10	7
Rat	91.3	5	Aerosol	10	10
Rat	4.3	30	Aerosol	10	1
Rat	6.6	30	Aerosol	10	0
Rat	9.0	30	Aerosol	10	6
Rat	9.8	30	Aerosol	10	8

3

4

5 **Probit function**

6 The probit function and associated LC-values have been calculated using the
7 DoseResp program (Wil ten Berge, December 2006) as:

$$8 \text{ Pr} = a + b \ln C + c \ln t + d \text{ PS}$$

9 Where C is concentration in mg/m³, t is exposure duration in minutes and

10 PS = physical state (gas/aerosol).

11

12 The LC₅₀ did not differ by more than a factor 2 between gas and aerosol exposure,
13 nor did analysis with physical state as covariate give any indication that differences
14 exist between gas and aerosol exposure. The authors also concluded that gas and
15 aerosol exposure produced the same lethality. For this reason the data from gas and
16 aerosol exposures were pooled and analysed to derive the animal probit function (last

1 column of table below). The results for gas and aerosol were derived from the
2 analysis with physical state as covariate and from pooled data.

3

4 Since only 2 exposure durations were tested in this study, the n-value is meaningless
5 and this study will be treated as a 30-minute lethality study. The LC₅₀ values
6 presented below were calculated with only the 30-minute data. The LC₅₀ value for the
7 combined gas/aerosol data will be used as a PoD for the probit calculation.

8

9

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Gas</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Aerosol</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Combined</i>
30	7132 (6156 -8172)	8329 (7209 - 9676)	7684 (6906 - 8496)

10

11

12

1 **Study ID: B1.2**

2

3 **Author, year: Darmer 1974**

4 Substance: Hydrogen Chloride

5 Species, strain, sex: Mouse, CF-1 ICR, sex unspecified

6 Number/sex/conc. group: 10-15 / concentration / time

7 Age and weight: 25-30 grams, unspecified age (adult as judged from
8 weight)

9 Observation period: 7 days

10

11 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time; many details (housing, lighting, food, water, etc) not specified</i>
Stability of test compound in test atmosphere	<i>Not specified. Exposure to gas in pre-dried air (for gas exposures), OR gas introduced in nearly saturated water droplet mist (for aerosol exposures).</i>
Use of vehicle (other than air)	<i>Air</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body, animals introduced in chamber with little air loss after chamber concentration equilibrated</i>
Type of restrainer	<i>No restrainer used – whole body</i>
Pressure distribution.	<i>No information on pressure distribution; reference to publication that mentions 0.05 cm negative water pressure in the chamber</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified; air sampling appears to take place in animal breathing zone.</i>
Number of air changes per hour	<i>Air flow = 10cfm = 283 l/min = 17 m³/h, chamber volume is approx 2 m³, air exchange rate = 8.5/h</i>
Equilibration time (t95)	<i>3 × (2000 l / 283 l/min) = 21 min.</i>
Start of exposure relative to equilibration	<i>Animals were introduced into the chamber by means of sliding cage 'drawers' in the wall of the chamber</i>
Actual concentration measurement	<i>Continuous during exposure with specific chloride ion electrode (in breathing zone)</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No gravimetric assessment of droplet size, but optical method (semi-quantitative). Estimated diameter < 2 µm (water droplet size = aerodynamic Diameter, no droplets >5 µm observed)</i>
Assessment of Reliability	B1.2 This study received B status because only 2 exposure durations were studied and aerosol exposure was not well quantified. Sufficient other A-studies available.

12

1 **Results**

Species	Concentration (mg/m ³)	Exposure duration (min)	Gas or aerosol	Lethality	
				Exposed	Lethal
Mouse	4864	5	Gas	10	1
Mouse	7691	5	Gas	10	1
Mouse	9340	5	Gas	10	2
Mouse	9743	5	Gas	10	0
Mouse	11438	5	Gas	10	6
Mouse	12259	5	Gas	10	2
Mouse	14100	5	Gas	10	5
Mouse	20756	5	Gas	10	6
Mouse	40257	5	Gas	15	13
Mouse	45600	5	Gas	15	13
Mouse	623	30	Gas	15	0
Mouse	1724	30	Gas	15	2
Mouse	4071	30	Gas	15	8
Mouse	4136	30	Gas	15	4
Mouse	4472	30	Gas	15	12
Mouse	4668	30	Gas	15	6
Mouse	6148	30	Gas	15	11
Mouse	6196	30	Gas	15	13
Mouse	8152	30	Gas	15	14
Species	Concentration (mg/ℓ)	Exposure duration (min)	Gas or aerosol	Lethality	
				Exposed	Lethal
Mouse	13.3	5	Aerosol	10	3
Mouse	14.8	5	Aerosol	10	3
Mouse	17.7	5	Aerosol	10	5
Mouse	22.0	5	Aerosol	10	9
Mouse	25.0	5	Aerosol	10	9
Mouse	27.6	5	Aerosol	10	10
Mouse	1.8	30	Aerosol	10	2
Mouse	3.1	30	Aerosol	10	5
Mouse	3.8	30	Aerosol	10	5
Mouse	4.0	30	Aerosol	10	5
Mouse	4.3	30	Aerosol	10	9
Mouse	4.5	30	Aerosol	10	7
Mouse	6.5	30	Aerosol	10	10

2
3

1 **Probit function**

2 The probit function and associated LC-values have been calculated using the
3 DoseResp program (Wil ten Berge, December 2006) as
4 $Pr = a + b \times Inc + c \times \ln T + d \times PS$, with PS = physical state (gas/aerosol).

5
6 The LC₅₀ did not differ by more than a factor 2 between gas and aerosol exposure,
7 nor did analysis with physical state as covariate give any indication that differences
8 exist between gas and aerosol exposure. The authors also concluded that gas and
9 aerosol exposure produced the same lethality. For this reason the data from gas and
10 aerosol exposures were pooled and analysed to derive the animal probit function (last
11 column of table below). The results for gas and aerosol were derived from the
12 analysis with physical state as covariate and from pooled data.

13
14 Since only 2 exposure durations were tested in this study, the n-value is meaningless
15 and this study will be treated as a 30-minute lethality study. The LC₅₀ values
16 presented below were calculated with only the 30-minute data. The LC₅₀ value for the
17 combined gas/aerosol data will be used as a PoD for the probit calculation.

18

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Gas</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Aerosol</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Combined</i>
30	4043 (3394 - 4648)	3122 (2500 - 3741)	3616 (3093 - 4081)

19

20

21

1 **Study ID: B1.3**

2

3 **Author, year: Jean et al. 2006**

4 Substance: Hydrogen Chloride

5 Species, strain, sex: Male and female Fischer 344 rats

6 Number/sex/conc. group: 5 animals / sex / concentration

7 Age and weight: 8-12 weeks, 100-210 gr. (males), 100-160 gr (females)

8 Observation period: 14 days

9

10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>According to US EPA GLP</i>
Study carried out according to guideline(s)	<i>study meets OECD 403 guideline.</i>
Stability of test compound in test atmosphere	<i>Stable</i>
Use of vehicle (other than air)	<i>Air</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>NA</i>
Pressure distribution.	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>No information</i>
Number of air changes per hour	<i>approx. 44 air changes / hour</i>
Equilibration time (t95)	<i>T₉₉ is stated to be 6 minutes</i>
Start of exposure relative to equilibration	<i>Animals were in the chamber when the exposure started, and withdrawn from the chamber after allowing at least 1 T₉₉ period to pass</i>
Actual concentration measurement	<i>While inlet and chamber concentrations were monitored, nominal concentrations were used for the calculations</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	B1.3 <i>Only 1 exposure duration, only LC₅₀ value described without individual concentration-lethality data</i>

11

12 This dataset is part of a study where the relative acute inhalation toxicities of a series
 13 of chlorosilanes is compared to the acute inhalation toxicity of HCl, aimed at building
 14 a prediction model for chlorosilane toxicity. The test conditions for the chlorosilanes
 15 have been described in some detail, the testing conditions for HCl have not. Since the
 16 study was well designed and described and since the comparability of tests across the
 17 tested chemicals is the main feature of the study, it is assumed that the test
 18 conditions for HCl are equal to those for the chlorosilanes.

19

20

1 **Results**

2 The study only reports the 1-hour LC50 value in rats, males and females combined.

3

4 **Probit function**5 No concentration-time-response probit function could be calculated from these data
6 alone.

7

8

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Male</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Female</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Combined</i>
60			5502 (4656 - 7691)

9

10

1 **Study ID: B1.4**2
3 **Author, year: Wohlslagel et al. 1976**

4 Substance: Hydrogen Chloride
 5 Species, strain, sex: Male rats, Sprague-Dawley
 6 Number/sex/conc. group: 10 males / concentration
 7 Age and weight: adult males, 250-325 gr.
 8 Observation period: 14 days

9
10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time.</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>No information</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>NA</i>
Pressure distribution	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>No information</i>
Number of air changes per hour	<i>airflow = 11 cubic feet/min in a 22.1 cubic feet chamber, which equals 30 air changes / hour</i>
Equilibration time (t95)	<i>6 minutes</i>
Start of exposure relative to equilibration	<i>Animals were inserted and withdrawn from the exposure chamber 'using a sliding cage drawer'. It is unclear how much clean air was introduced with each opening of the chamber.</i>
Actual concentration measurement	<i>Continuous analysis with ion specific (and reference) electrode</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	B1.4 <i>Only 1 exposure duration, details about exposure conditions missing</i>

11
12 **Results**

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			exposed	responded
rat	2756	60	10	0
rat	3929	60	10	2
rat	4976	60	10	6
rat	5990	60	10	8
rat	6772	60	10	10

1 **Probit function**

2 No concentration-time-response probit function could be calculated from these data
3 alone. Data were only available for a 1 hour time period. Therefore only the 1 hour
4 LC₅₀ value was calculated and presented in the table below.

5
6

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Male</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Female</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Combined</i>
60	4748 (4174 - 5246)		

7
8

1 **Study ID: B1.5**

2
3 **Author, year: Wohlslagel 1976**

4 Substance: Hydrogen Chloride
5 Species, strain, sex: Male mice, CF-1 ICR
6 Number/sex/conc. group: 10 males / concentration
7 Age and weight: adult males, 25-32 gr.
8 Observation period: 14 days

9
10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time.</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>No information</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>NA</i>
Pressure distribution.	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>No information</i>
Number of air changes per hour	<i>airflow = 11 cubic feet/min in a 22.1 cubic feet chamber which equals 30 air changes / hour</i>
Equilibration time (t95)	<i>6 minutes</i>
Start of exposure relative to equilibration	<i>Animals were inserted and withdrawn from the exposure chamber 'using a sliding cage drawer'. It is unclear how much clean air was introduced with each opening of the chamber.</i>
Actual concentration measurement	<i>Continuous analysis with ion specific (and reference) electrode</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	B1.5 <i>Only 1 exposure duration, details about exposure conditions missing</i>

11
12 **Results**

13

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			exposed	responded
mouse	847	60	10	2
mouse	1497	60	10	3
mouse	2108	60	10	6
mouse	2891	60	10	8
mouse	3764	60	10	10

1 **Probit function**

2 No concentration-time-response probit function could be calculated from these data
3 alone. Data were only available for a 1 hour time period. Therefore only the 1 hour
4 LC₅₀ value was calculated and presented in the table below.

5

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Male</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Female</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Combined</i>
60	1684 (1219 - 2138)		

6

7

1 **Study ID: B1.6**2 **Author, year: Higgins 1972**

3 Substance: Hydrogen Chloride

4 Species, strain, sex: Rat, Wistar, sex unspecified

5 Number/sex/conc. group: 5 / concentration

6 Age and weight: 250 - 275 grams (adult as judged from body weight)

7 Observation period: 7 days

8

9 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>GLP did not exist at the time</i>
Study carried out according to guideline(s)	<i>OECD 403 did not exist at the time.</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>Air</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>NA</i>
Pressure distribution.	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>No information - 1 sampling location</i>
Number of air changes per hour	<i>No information (other than mention of dynamic flow system)</i>
Equilibration time (t95)	<i>unspecified</i>
Start of exposure relative to equilibration	<i>after complete equilibration a cage containing all 10 animals was quickly introduced in the chamber, and quickly pulled out after 5 minutes exposure</i>
Actual concentration measurement	<i>Specific ion electrode after capture in aqueous solution</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	B1.6 Only 1 exposure duration, relatively short observation period.

10

11

12 **Results**

13

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			Exposed	Dead
Rat	45600	5	10	0
	48640	5	10	1
	60572	5	10	6
	68704	5	10	7
	87081	5	10	9

14

15

1 **Probit function**

2 No concentration-time-response probit function could be calculated from these data
3 alone. Data were only available for a 5-min time period. Therefore only the 5-min
4 LC₅₀ value was calculated and presented in the table below.

5

6

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Male</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Female</i>	<i>LC₅₀ (mg/m³) 95%-C.I. Sex unknown</i>
5			62,220 (56770 - 69150)

7

8 In this study the 5-min LC₅₀ for mice was also determined, and was calculated to be
9 20,900 mg/m³ (15,700 - 27800 mg/m³).

10

11

12

13

1 **Study ID: C.1**

2

3 **Author, year: Kaplan 1988**

4 Substance: Hydrogen Chloride

5 Species, strain, sex: male baboons

6 Number/sex/conc. group: 3 / concentration

7 Age and weight: adult, 7.1-13.1 kg

8 Observation period: 3 months

9

10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to guideline(s)	<i>No mention of guideline OECD 403. Study was not aimed at determining acute lethality. Light/dark cycle, temperature, humidity and food/water provision consistent with OECD guideline 403 criteria.</i>
Stability of test compound in test atmosphere	<i>No information. Deposition of HCl on the walls of the exposure chamber was mentioned.</i>
Use of vehicle (other than air)	<i>Air with 50% rel. hum.</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Head only</i>
Pressure distribution.	<i>Test chamber was kept at -0.6 mm water pressure</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>1 sampling location.</i>
Number of air changes per hour	<i>Airflow of 40 l/min through 200 l chamber, i.e. 12 air changes/hour</i>
Actual concentration measurement	<i>Continuous monitoring: continuous titration (AFNOR French standard FD X70101, 1982) or microconductivity detector to maintain a constant exposure level. Analytical determination of actual exposure level by titration of HCl adsorbed on dry soda lime sampling tubes (5 fixed time intervals of 3 min).</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	C Data do not allow to calculate an LC ₅₀ , but study provides essential supporting information

11

12

13

1 **Results**

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality Male
Baboon	0	15	0
Baboon	787-885	15	0
Baboon	5259-7001	15	0
Baboon	12920-17580	15	0

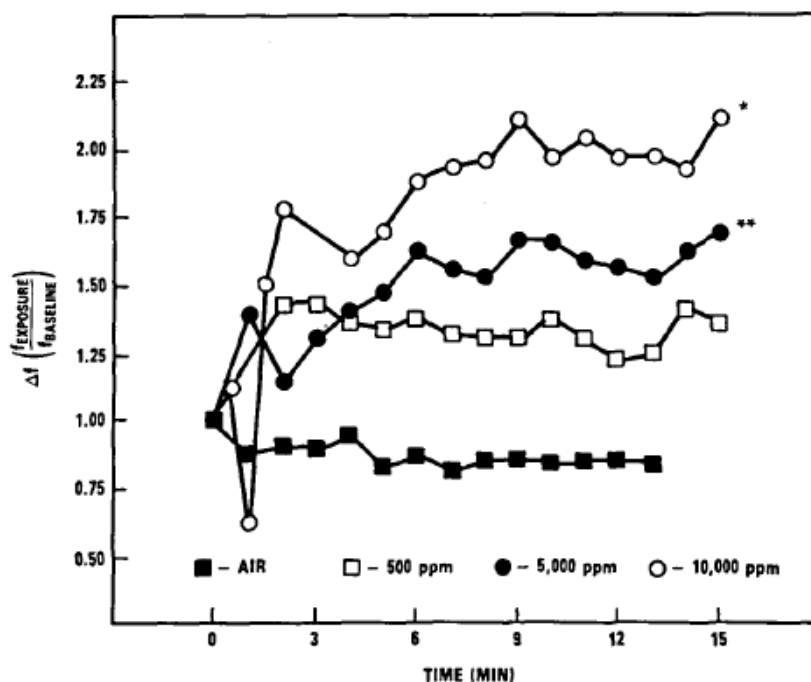
2

3 Respiratory rate (f), tidal volume (V_T), and Minute Volume (MV) were measured and
 4 recorded before (5 min), during (15 min) and after (15 min) exposure of the
 5 anesthetized baboons (13 mg/kg ketamine). Arterial blood samples were obtained
 6 from a catheter in the femoral artery once before exposure, every minute during
 7 exposure and every 5 minutes after exposure until the animal's appearance was
 8 normal. Pulmonary function tests were performed in the week before, 3 days and 3
 9 months after exposure.

10

11 After initiation of exposure, baboons held their breath for 10-20 seconds and then
 12 increased their respiratory rate (figure 2 taken from Kaplan et al), while tidal volume
 13 remained unaffected.

14



15 **FIGURE 2.** Change in respiratory rate (f) of the baboon during a 15-min exposure to air or HCl
 16 atmospheres; Δf is the ratio of f during exposure to the baseline f during the 5 min prior to
 17 exposure. Data points are average values of three animals. Asterisk, significantly different
 18 ($p \leq 0.05$) from control (air) and 500 ppm HCl. Double asterisk, significantly different ($p \leq 0.05$)
 19 from control (air).

15

16

17 Minute volume also increased with exposure level (figure 3 from Kaplan et al). The
 18 tested HCl exposures did not cause any significant alterations in any of the pulmonary
 19 function parameters in any of the HCl exposed groups at 3 days or 3 months following
 20 exposure.

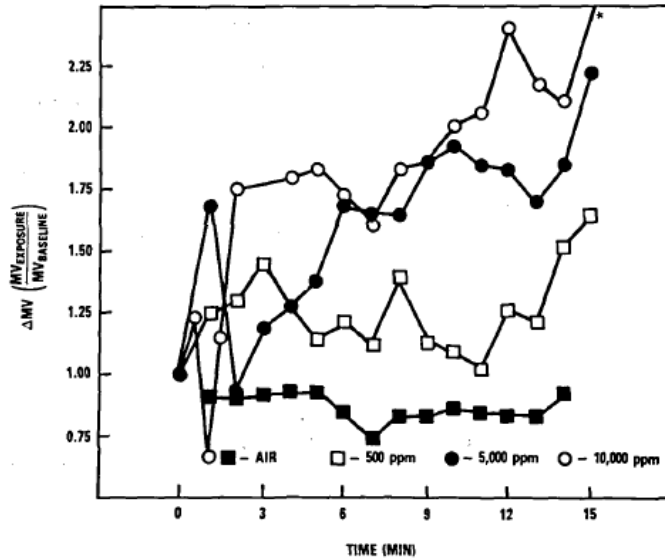


FIGURE 4. Change in minute volume (MV) of the baboon during a 15-min exposure to air or HCl atmospheres; ΔMV is the ratio of MV during exposure to the baseline MV during the 5 min prior to exposure. Data points are average values of three animals. Asterisk, significantly different ($p \leq 0.05$) from control (air).

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Despite the increased respiratory frequency and minute volume in response to HCL inhalation, arterial PaO_2 values decreased rapidly in animals exposed to $\pm 6000 \text{ mg/m}^3$ and to $\pm 15000 \text{ mg/m}^3$.

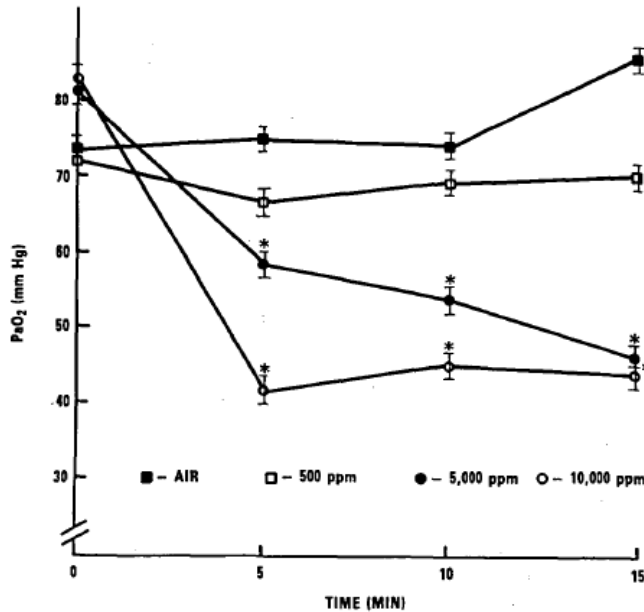


FIGURE 5. Arterial PaO_2 of the baboon during a 15-min exposure to air or HCl atmospheres. Values are means \pm SD of three animals. Asterisk, significantly different ($p \leq 0.05$) from preexposure, control, and 500-ppm values.

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The data suggest a possibly increased Minute Volume response at 3 months past exposure to $\pm 6000 \text{ mg/m}^3$ and $\pm 15000 \text{ mg/m}^3$ to a CO_2 challenge (high variability, small groups).

1 **Study ID: C.2**

2

3 **Author, year: Kaplan 1993**

4 Substance: Hydrogen Chloride

5 Species, strain, sex: male baboons

6 Number/sex/conc. group: 3 / concentration

7 Age and weight: adult, 7.1-13.1 kg

8 Observation period: 1 year

9

10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to guideline(s)	<i>No mention of guideline OECD 403. Study was not aimed at determining acute lethality. Light/dark cycle, temperature, humidity and food/water provision consistent with OECD guideline 403 criteria.</i>
Stability of test compound in test atmosphere	<i>No information. Deposition of HCl on the walls of the exposure chamber was mentioned.</i>
Use of vehicle (other than air)	<i>Air with 50% rel. hum.</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Head only</i>
Pressure distribution.	<i>Test chamber was kept at -0.6 mm water pressure</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>1 sampling location.</i>
Number of air changes per hour	<i>Airflow of 40 l/min through 200 l chamber, i.e. 12 air changes/hour</i>
Actual concentration measurement	<i>Continuous monitoring: continuous titration (AFNOR French standard FD X70101, 1982) or microconductivity detector to maintain a constant exposure level. Analytical determination of actual exposure level by titration of HCl adsorbed on dry soda lime sampling tubes (5 fixed time intervals of 3 min).</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	C Data do not allow to calculate an LC ₅₀ , but study provides essential supporting information

11

12 This is essentially the same study as Kaplan *et al* 1988, but with an observation
 13 period extended to 1 year. The upper respiratory tract (biopsy) and lung tissue from
 14 the right middle lobe of the lungs (lobectomy) of baboons exposed to 0 (control),
 15 $\pm 6000 \text{ mg/m}^3$ and $\pm 15000 \text{ mg/m}^3$ were studied with light microscopic examination.
 16

- 1 Significant histopathological changes were only observed in animals exposed to
2 $\pm 15000 \text{ mg/m}^3$; the most significant abnormality consisted of fibrosis of the
3 pulmonary parenchyma and pleura.
4
5 In 2/3 animals exposed to $\pm 6000 \text{ mg/m}^3$ mild or minimal patchy atelectasis and
6 minimal mucinous exudate in smaller bronchi or bronchioles were the principal
7 findings.
8 No histopathological changes were found in the biopsy samples of the respiratory
9 tract at any of the exposure conditions.
10
11 No chest X-ray changes were observed in any of the animals within 1 hour following
12 the exposure.
13
14
15

1 **Study ID: C.3**

2

3 **Author, year: Kaplan 1985**

4 Substance: Hydrogen Chloride

5 Species, strain, sex: male baboons and rats

6

7 Kaplan *et al* also performed a study to determine escape impairment of HCl exposure
8 in rats and baboons. Animals were used for more than one exposure, and the
9 exposure was influenced by the animal's response (escape or avoidance). These data
10 do not provide quantitative exposure-lethality information.

11

12

1 **Study ID: C.4**

2
3 **Author, year: Burleigh 1985**

4 Substance: Hydrogen Chloride

5 Species, strain, sex: Guinea pig, males

6 Number/sex/concentration group: 4-8 / concentration

7 Age and weight: adult, 330 - 450gr

8 Observation period: no information

9
10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to guideline(s)	<i>No information</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>No information</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Head only</i>
Pressure distribution.	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>No information</i>
Number of air changes per hour	<i>20 1/min</i>
Actual concentration measurement	<i>Colorimetric analysis</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	C Only 1 exposure duration, data do not allow to calculate an LC ₅₀ .

11
12
13 **Results**

14 Taken from Busschers et al (2002)

15

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			Male	Female
Guinea pig	0	30	0/4	
	477	30	0/4	
	1013	30	0/4	
	1550	30	2/8	
	2055	30	3/8	

1 **Study ID: C.5**2
3 **Author, year: Malek 1989**

4 Substance: Hydrogen Chloride

5 Species, strain, sex: Guinea pig, males

6 Number/sex/concentration group: 2-4 / concentration

7 Age and weight: adult, 325 - 400gr

8 Observation period: no information

9
10 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to guideline(s)	<i>No information</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>No information</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body with moderate exercise</i>
Pressure distribution.	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>No information</i>
Number of air changes per hour	<i>8 1/min, chamber size uncertain</i>
Actual concentration measurement	<i>Impingers, sampling port in exposure chamber</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	C Only 1 exposure duration, data do not allow to calculate an LC ₅₀ .

11
12
13 **Results**

14 Taken from Busschers et al (2002)

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			Male	Female
Guinea pig	163	30	0/3	
	213	16.5	0/3	
	246	1.3	0/2	
	891	0.65	4/4	

1 **Study ID: C6**2
3 **Author, year: Siddiqui 1999**4 Substance: Hydrogen Chloride
5 Species, strain, sex: Rat, Sprague-Dawley
6 Number/sex/conc. group: 5 / sex / concentration
7 Age and weight: adult, 144 - 300 gr
8 Observation period: 14 days
910 **Evaluation of study quality**

Criteria	Comment
Study carried out according to GLP	<i>No GLP statement provided</i>
Study carried out according to guideline(s)	<i>No information</i>
Stability of test compound in test atmosphere	<i>No information</i>
Use of vehicle (other than air)	<i>No information</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Type of restrainer	<i>N/A, whole-body exposure</i>
Pressure distribution	<i>Test chamber was kept at -0.6 mm water</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not provided - only 1 sampling location and no additional information to confirm or reject homogeneity of the test atmosphere.</i>
Number of air changes per hour	<i>Not provided</i>
Equilibration time (t95)	<i>t95 in minutes - unknown</i>
Start of exposure relative to equilibration	<i>Unknown</i>
Actual concentration measurement	<i>Every 10 min with FT-IR analyzer</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>No information</i>
Assessment of Reliability	C Only 1 exposure duration, essential study information lacking.

11
12
13 **Results**14 The results of this study are taken from Busschers *et al* (2002). The original report
15 has not been obtained.
16

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
			Male	Female
Rat	3659	60	1/5	0/5
	4822	60	4/5	0/5
	5662	60	3/5	4/5

1 **Probit function**

2 No concentration-time-response probit function could be calculated from these data
3 alone. Data were only available for a 1 hour time period. Therefore only the 1 hour
4 LC₅₀ value was calculated and presented in the table below.

5
6

<i>Duration (minutes)</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Male</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Female</i>	<i>LC₅₀ (mg/m³) 95%- C.I. Combined</i>
60			5044 (4376 - 6480)

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8

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