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

Probit function technical support document

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Status: Interim
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substance name	CAS number
Nickel tetracarbonyl	13463-39-3

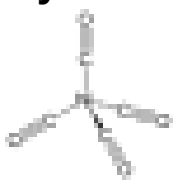
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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/.

Technical support document Nickel tetracarbonyl



1. Substance identification

CAS-number:	13463-39-3
IUPAC name:	Nickel tetracarbonyl
Synonyms:	Nickel carbonyl, tetracarbonyl nickel
Molecular formula:	C_4NiO_4
Molecular weight:	170.8 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	43°C (at 101.3 kPa)
Vapour pressure:	42.8 kPa (at 20°C)
Saturated vapour conc:	428000 ppm = 3041 g/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.141 ppm (at 20°C and 101.3 kPa)
	1 ppm = 7.105 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H330-351-360D

2. Mechanism of action and toxicological effects following acute exposure[1]

Acute effects: The primary target of nickel tetracarbonyl-induced acute toxicity appears to be the lungs. Human case studies have shown that a latency period often occurs between initial signs of toxicity and subsequent serious effects that may progress to death. Nickel tetracarbonyl may induce bronchoconstriction and depression of the central nervous system (CNS). Signs and symptoms of high exposure are chest pains, dyspnea, and cyanosis progressing to lung oedema, pneumonia, delirium and convulsions.

Long-term effects: Chronic exposure to nickel tetracarbonyl at relatively low exposure levels produced effects in the respiratory tract in a worker population. Nickel tetracarbonyl has a harmonized classification for carcinogenicity as Carc. 2 (H351: Suspected of causing cancer).

3. Human toxicity data

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

4. Animal acute toxicity data

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

1. AEGL final TSD, ERPG document and EU RAR and reference database for nickel tetracarbonyl, covering references before and including 1995.
2. An additional search covering publications from 1980 onwards was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, ECHA, RTECS, IRIS and ToxNet with the following search terms:
   - Substance name and synonyms
   - CAS number
   - lethal*
   - mortal*
   - fatal*
   - LC_{50}, LC
   - probit
3. Unpublished data were sought through networks of toxicological scientists.

[1] AEGL final 2007.

Animal lethal toxicity data focused on acute exposure are described in Appendix 1. A total of 8 studies were identified -with 12 datasets for 4 species- with data on lethality following acute inhalation exposure. None of the datasets was assigned status A for deriving the human probit function, 5 datasets were assigned status B and 7 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

Studies on sensory irritation were not found.

5. Probit functions from individual studies

All available acute lethality data on nickel tetracarbonyl are displayed in Figure 1.

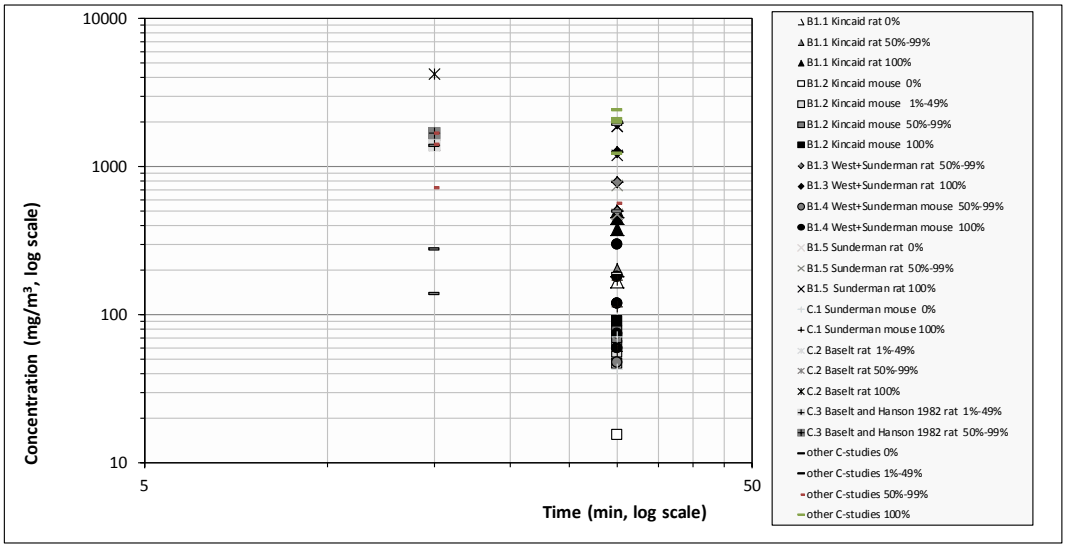


Figure 1 *All available acute lethality data for nickel tetracarbonyl.*

The data that were selected for initial analysis of the animal probit function are presented in Table 1 and Figure 2.

It was possible to derive a probit function for nickel tetracarbonyl based on the available studies with B1 quality by pooling data. Therefore, the probit function was derived using data from the studies with B1 quality, none of which enabled to produce a concentration-time-lethality relationship.

Probit functions have been calculated and reported in Appendix 1 for each of the reported studies. The results of the calculations are presented in Table 1.

Table 1 *Data selected for initial analysis of the animal probit function of nickel tetracarbonyl.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	n-value 95% C.I.
B1.1	Rat	30-min LC_{50}	235 (175-281)	N/A
B1.2	Mouse	30-min LC_{50}	69 (64-76)	N/A
B1.3	Rat	30-min LC_{50}	361 (126-486)	N/A
B1.4	Mouse	30-min LC_{50}	48 (C.I. could not be calculated)	N/A

B1.5	Rat	30-min LC_{50}	373 (210-468)	N/A

The data of rat studies B1.1, B1.3, and B1.5 and mouse studies B1.2, and B1.4 are presented graphically below.

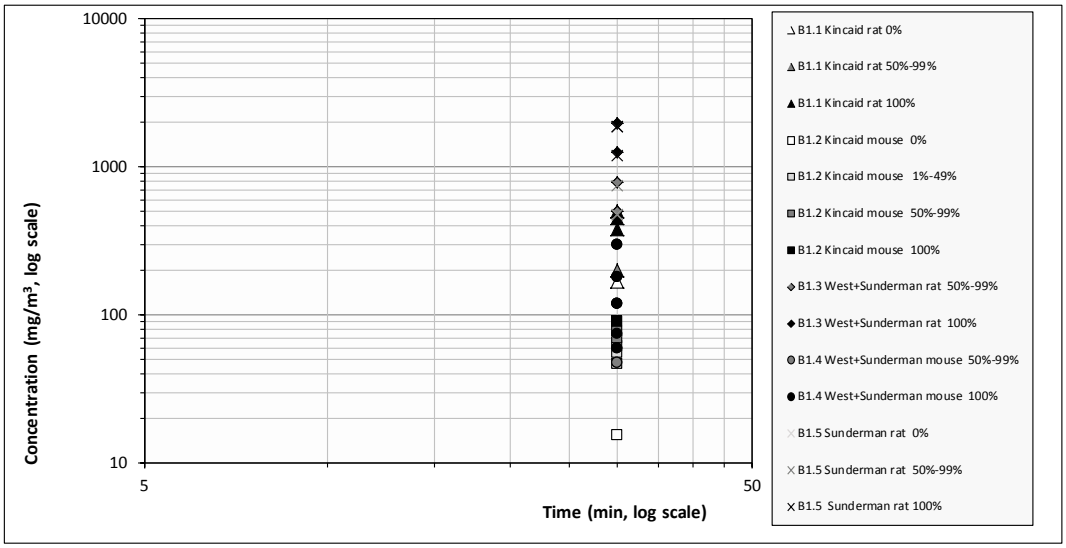


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of nickel tetracarbonyl.*

Mice appear to be more susceptible to the acute effects of nickel tetracarbonyl exposure than rats. Information on the slope is not available as no C x t studies are included in the database. Therefore, no definite conclusion can be drawn whether or not the data of the different species (rat and mouse) converge.
However, given that no data from other species (for example non-human primates) are available to support excluding a specific species, data of both rat and mouse were used.
Rat studies B1.3 and B1.5 included a relatively short post-exposure observation period of five days only. However, this is considered acceptable given that Kincaid *et al*. (1953) stated that deaths occurred within 2-3 days after exposure.
The data from all rat and mouse B1 studies (i.e. rat studies B1.1, B1.3 and B1.5 and mouse studies B1.2 and B1.4) were therefore selected for the final dataset for the derivation of the animal probit function.

Figure 3 provides an overview of LC_{50} values and LC_{50}-time relationships for all studies in the final analysis. The data that were selected for final analysis of the animal probit function are presented in Table 2 and Figure 4.

The final data for calculating the animal probit function contains 5 datasets from 3 studies and includes data from 2 animal species.

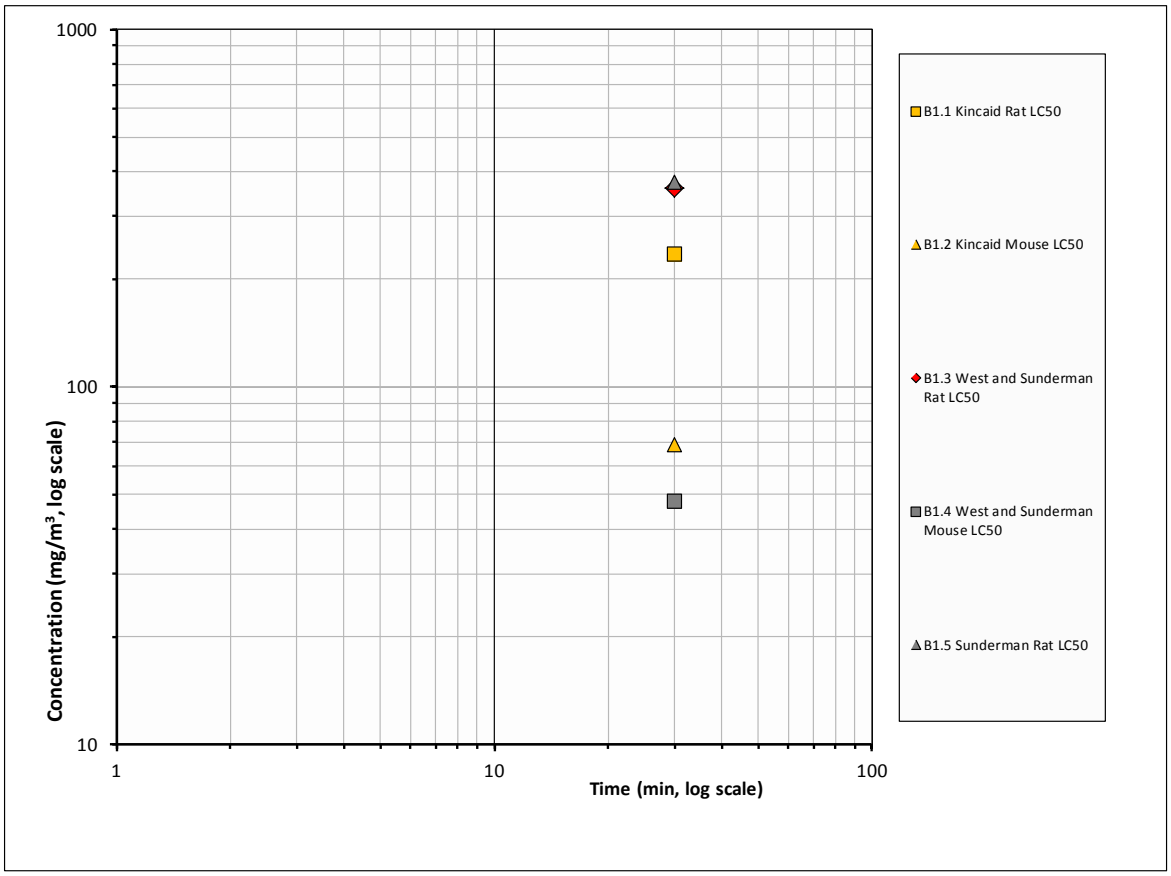


Figure 3 *LC_{50} values of B1 datasets for nickel tetracarbonyl, over time where available.*

Table 2 *Data selected for the derivation of the animal probit function of nickel tetracarbonyl (identical to Table 1)*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	n-value 95% C.I.
B1.1	Rat	30-min LC_{50}	235 (175-281)	N/A
B1.2	Mouse	30-min LC_{50}	69 (64-76)	N/A
B1.3	Rat	30-min LC_{50}	361 (126-486)	N/A
B1.4	Mouse	30-min LC_{50}	48 (C.I. could not be calculated)	N/A
B1.5	Rat	30-min LC_{50}	373 (210-468)	N/A

The data of the selected datasets are presented graphically below.

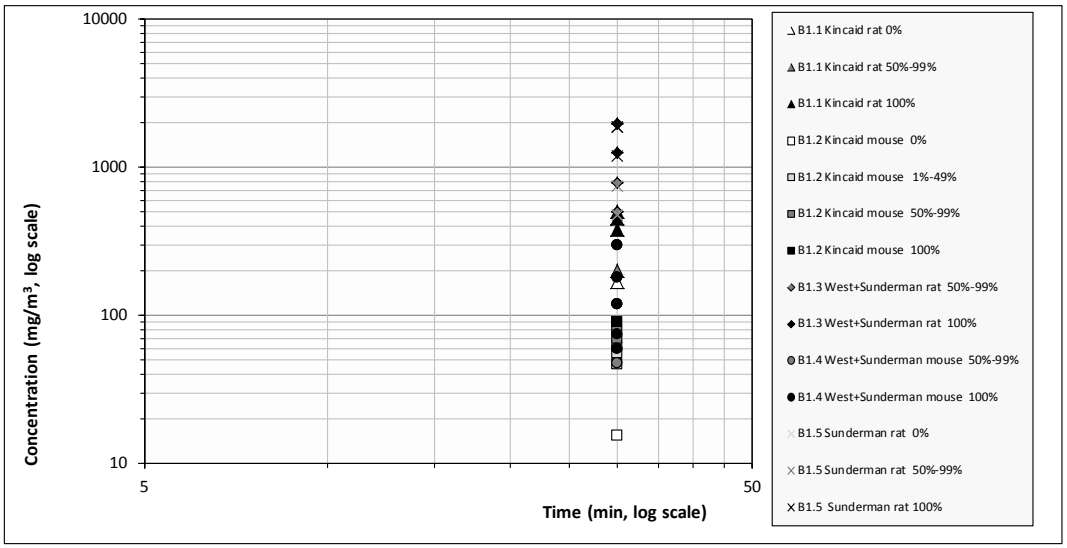


Figure 4 Final data selected for derivation of the animal probit function of nickel tetracarbonyl (identical to figure 2).

6. Derivation of the human probit function

To derive the human probit function, the results from rat studies B1.1, B1.3, B1.5 and mouse studies B1.2 and B1.4 have been used to derive a point of departure.

No substance-specific value for n was available. Therefore, the default value of 2 is used.
LC_{50} values of the available B1 studies were all for the common exposure duration of 30 minutes.

The species-specific geometric mean LC_{50}-values were calculated from all available (time-scaled) LC_{50} values of rat studies B1.1, B1.3, B1.5 and mouse studies B1.2 and B1.4. The 30-min species-specific LC_{50}-values were 316 mg/m^3 for rats and 57.6 mg/m^3 for mice (inner multiplication from i=1 tot 2 in the formula below. The geometric mean overall time scaled LC_{50}-value was calculated as follows (outer multiplication from j=1 to 2 in the formula below):

$$\overline{LC_{50}} = \left[\prod_{j=1}^{s}\left(\prod_{i=1}^{m} LC_{50,i}\right)^{1/m}\right]^{(1/s)}$$

With $\overline{LC_{50}}$ = geometric mean LC_{50}-value across species
$LC_{50,i}$ = LC_{50}-value of study i.
m = number of observations on LC_{50}-values within a species (i=1…m).
s = number of species for which LC_{50}-values are pooled (j= 1…s).

The Point of Departure for the human probit function is a 30-minute geometric mean animal LC_{50} value of 135 mg/m^3.

The human equivalent LC_{50} was calculated by applying the following assessment factors:

Table 3 *Rationale for the applied assessment factors.*

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	3	Default
Nominal concentration	1	Rat study B1.1 and mouse study B1.2 presented no actual concentrations but nominal concentrations, however these were < 25% of the saturated vapour concentration. Other selected studies presented actual concentrations.
Adequacy of database:	1	Five B1 studies used for the final analysis.

The estimated human equivalent 30-minute LC_{50} value is 135 / 3 = **45 mg/m^3**.

No reliable experimentally determined n-value was available, so the default n-value of **2** was used. Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.0**.

The human probit function is then calculated on the human equivalent 30 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1.0 \times \ln (45^2 \times 30)$ resulting in the a-value of **-6.01**.

$Pr = -6.01 + 1.0 \times \ln (C^2 \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has a scientifically sound basis. The probit function is based on three studies in the rat and two studies in the mouse with B1 quality. Further, these data included in total 40 C x t combinations, all with 30 minute exposure duration and lethality in the range of 0-100%.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 7 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 10 mg/m^3.

Table 4 *LC-vales calculated with the derived probit function compared with existing acute inhalation exposure guidelines.*

Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
0.1% lethality, this probit	10	7
1% lethality, this probit	14	10
AEGL-3[2] (2007, final)	2.3	1.1
ERPG-3[2]	-	-
LBW (2015)	2.2	1.1

Compared with equivalent (inter)national guideline levels as presented in the table above, the lethal levels derived with this probit function are of the same order of magnitude.

[2] AEGL and ERPG values were converted from ppm to mg/m^3 with the conversion factor calculated in section 1. Therefore, the AEGL and ERPG values in mg/m^3 can deviate slightly from those reported in the AEGL and ERPG TSDs.

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: Kincaid et al. 1953

Substance: Nickel tetracarbonyl
Species, strain, sex: Rat, Wistar albino
Number/sex/concentration group: 6-21/group, sex not specified
Age and weight: Not specified
Observation period: No period specified. After exposure, the experimental animals (described for mice and rats) returned to their cages immediately after exposure, and were allowed to stay there undisturbed until death or complete recovery occurred.

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the time
Study carried out according to OECD guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	Experiments independently carried out showed that nickel tetracarbonyl in air at room temperature decomposed by not more than 5% in 50 seconds.
Use of vehicle (other than air)	Absolute alcohol
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution.	No information
Homogeneity of test atmosphere in breathing zone of animals	A solution of 1 to 10% nickel tetracarbonyl in absolute alcohol was introduced into a syringe, which introduced the solution in a metered air stream. The metered air was provided at a predetermined rate by a pump. Evaporation was immediate. No information on homogeneity at breathing zone.
Number of air changes per hour	Flow ranged from 600 to 1900 liters per hour. Chamber volume was 8 liters, resulting in 75 to 238 air changes per hour. It is noted that the chamber volume was small in relation to the number of animals per group (6-21). Inlet at the bottom, outlet at the top of the inhalation chamber.
Equilibration time (t95)	0.76 – 2.4 min
Start of exposure relative to equilibration	Not specified
Actual concentration measurement	Nominal concentrations were given based on airflow and injected substance.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A

Assessment of Reliability	**B1** Study was well performed. Limited to one exposure duration; no actual concentrations presented, though nominal concentrations calculated. Nominal concentrations were < 25% of the saturated vapour concentration.

Additional remark: The study authors presented information on the time of death as follows: "In the animals that succumbed, death usually occurred two to three days after exposure".

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Rat	0.17×10^3	N/A	30	0/6
	0.20×10^3	N/A	30	9/18
	0.38×10^3	N/A	30	17/21
	0.45×10^3	N/A	30	15/18
	0.50×10^3	N/A	30	12/12

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Rat	-5.54	1.93	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
30	235 (175-281)

No C × t probit function could be calculated from these data alone.

Study ID: B1.2

Author, year: Kincaid et al. 1953

Substance: Nickel tetracarbonyl
Species, strain, sex: Mouse, albino
Number/sex/concentration group: 10-29/group, sex not specified
Age and weight: Not specified
Observation period: No period specified. After exposure, the experimental animals (specifically described for mice and rats) returned to their cages immediately after exposure, and were allowed to stay there undisturbed until death or complete recovery occurred.

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the time
Study carried out according to OECD guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	Experiments independently carried out showed that nickel tetracarbonyl in air at room temperature decomposed by not more than 5% in 50 seconds.
Use of vehicle (other than air)	Absolute alcohol
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution.	No information
Homogeneity of test atmosphere in breathing zone of animals	A solution of 1 to 10% nickel tetracarbonyl in absolute alcohol was introduced into a syringe, which introduced the solution in a metered air stream. The metered air was provided at a predetermined rate by a pump. Evaporation was immediate. No information on homogeneity at breathing zone.
Number of air changes per hour	Flow ranged from 600 to 1900 liters per hour. Chamber volume was 8 liters, resulting in 75 to 238 air changes per hour. Inlet at the bottom, outlet at the top of the inhalation chamber.
Equilibration time (t95)	0.76 – 2.4 min
Start of exposure relative to equilibration	Not specified
Actual concentration measurement	Nominal concentrations were given based on airflow and injected substance.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A

Assessment of Reliability	**B1** Study was well performed. Limited to one exposure duration. No actual concentrations presented, though nominal concentrations calculated. Nominal concentrations were < 25% of the saturated vapour concentration.

Additional remark: The study authors presented information on the time of death as follows: "In the animals that succumbed, death usually occurred two to three days after exposure".

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Mouse	15.5	N/A	30	0/12
	46.5	N/A	30	2/15
	56	N/A	30	3/10
	62	N/A	30	10/29
	70	N/A	30	10/20
	78	N/A	30	12/22
	90	N/A	30	10/10

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Mouse	-8.61	3.21	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
30	69 (64-76)

No C × t probit function could be calculated from these data alone.

Study ID: B1.3

Author, year: West and Sunderman (1958)
Substance: Nickel tetracarbonyl
Species, strain, sex: Rat, Wistar. Sex not specified
Number/sex/concentration group: 10/group
Age and weight: not specified
Observation period: 5 days

Evaluation of study quality*

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the time
Study carried out according to OECD guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	Not specified
Use of vehicle (other than air)	Mixture of equal parts of ethyl alcohol and ether
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution.	Negative
Homogeneity of test atmosphere in breathing zone of animals	A solution of nickel carbonyl was introduced into a syringe, which introduced the solution in a metered air stream. Evaporation was immediate. Air was introduced at one of the upper corners of the chambers and withdrawn at the diametrically opposite corner.
Number of air changes per hour	The number of exact air changes per hour is not stated. The aim was to use an airflow of 550 L/min in the chamber of 539 L, resulting in approximately 60 air changes per hour.
Equilibration time (t95)	Approximately 3 minutes
Start of exposure relative to equilibration	At start of concentration build-up
Actual concentration measurement	Continuous measurement of the concentration of nickel carbonyl present in the chamber was made throughout the 30-minute exposure period. Reference was given to Kincaid *et al*. 1956, who described two colorimetric methods for low and high nickel tetracarbonyl levels.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A
Assessment of Reliability	**B1** Study was well performed. Limited to one exposure duration.

* information on the experimental design of the study was obtained from Sunderman *et al*. (1956)

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Rat	0.50×10^3	NA	30	7/10
	0.50×10^3	NA	30	6/10
	0.79×10^3	NA	30	9/10
	0.79×10^3	NA	30	7/10
	1.26×10^3	NA	30	10/10
	1.26×10^3	NA	30	10/10
	1.99×10^3	NA	30	10/10
	1.99×10^3	NA	30	10/10
	0.50×10^3	NA	30	9/10
	1.99×10^3	NA	30	10/10

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Rat	-4.23	1.57	-

The LC_{50} values given below are subject to large uncertainty since the mortality range was > 50% to 100%.

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
30	361 (126-486)

No C × t probit function could be calculated from these data alone.

Study ID: B1.4

Author, year: West and Sunderman (1958)
Substance: Nickel tetracarbonyl
Species, strain, sex: Mouse, C57. Sex not specified
Number/sex/concentration group: 10/group
Age and weight: not specified
Observation period: 5 days

Evaluation of study quality*

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the time
Study carried out according to OECD guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	Not specified
Use of vehicle (other than air)	Mixture of equal parts of ethyl alcohol and ether
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution.	Negative
Homogeneity of test atmosphere in breathing zone of animals	A solution of nickel carbonyl was introduced into a syringe, which introduced the solution in a metered air stream. Evaporation was immediate. Air was introduced at one of the upper corners of the chambers and withdrawn at the diametrically opposite corner.
Number of air changes per hour	The number of exact air changes per hour is not stated. The aim was to use an airflow of 550 L/min in the chamber of 539 L, resulting in approximately 60 air changes per hour.
Equilibration time (t95)	Approximately 3 minutes
Start of exposure relative to equilibration	At start of concentration build-up
Actual concentration measurement	Continuous measurement of the concentration of nickel carbonyl present in the chamber was made throughout the 30-minute exposure period. Reference was given to Kincaid *et al*. 1956, who described two colorimetric methods for low and high nickel tetracarbonyl levels.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A
Assessment of Reliability	**B1** Study was well performed. Limited to one exposure duration.

* information on the experimental design of the study was obtained from Sunderman *et al*. (1956)

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Mouse	0.048×10^3	NA	30	7/10
	0.048×10^3	NA	30	9/10
	0.06×10^3	NA	30	10/10
	0.06×10^3	NA	30	10/10
	0.075×10^3	NA	30	10/10
	0.12×10^3	NA	30	10/10
	0.12×10^3	NA	30	10/10
	0.12×10^3	NA	30	30/30
	0.18×10^3	NA	30	10/10
	0.18×10^3	NA	30	10/10
	0.30×10^3	NA	30	10/10
	0.30×10^3	NA	30	10/10

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Mouse	-425	111	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
30	48 (C.I. could not be calculated)

The confidence interval of the LC_{50} value could not be determined, probably since the mortality range was > 50% to 100%.

No C × t probit function could be calculated from these data alone.

Study ID: B1.5

Author, year: Sunderman 1964

Substance: Nickel tetracarbonyl
Species, strain, sex: Rat, Wistar, sex not specified
Number/sex/concentration group: 4 groups of 30 animals/group and 2 groups of 10 animals/group
Age and weight: not specified
Observation period: five days

Evaluation of study quality*

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the
Study carried out according to OECD guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	No information
Use of vehicle (other than air)	Mixture of equal parts of ethyl alcohol and ether
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution.	Negative
Homogeneity of test atmosphere in breathing zone of animals	A solution of nickel carbonyl was introduced into a syringe, which introduced the solution in a metered air stream. Evaporation was immediate. Air was introduced at one of the upper corners of the chambers and withdrawn at the diametrically opposite corner.
Number of air changes per hour	The number of exact air changes per hour is not stated. The aim was to use an airflow of 550 L/min in the chamber of 539 L, resulting in approximately 60 air changes per hour.
Equilibration time (t95)	Approximately 3 minutes
Start of exposure relative to equilibration	At start of concentration build-up
Actual concentration measurement	Continuous measurement of the concentration of nickel carbonyl present in the chamber was made throughout the 30-minute exposure period. Reference was given to Kincaid *et al*. 1956, who described two colorimetric methods for low and high nickel tetracarbonyl levels.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A
Assessment of Reliability	**B1** Study was well performed. Limited to one exposure duration.

* information on the experimental design of the study was obtained from Sunderman *et al*. (1956)

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Rat	476	NA	30	19/30
	746	NA	30	24/30
	1194	NA	30	30/30
	1890	NA	30	30/30
	476	NA	30	3/10
	1890	NA	30	9/10

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Rat	-5.08	1.70	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
30	373 (210-468)

No C × t probit function could be calculated from these data alone.

Study ID: C.1

Author, year: Sunderman 1964

Substance: Nickel tetracarbonyl
Species, strain, sex: Mouse, C57, sex not specified
Number/sex/concentration group: 4 groups of 30 animals/group and 1 group of 390 animals/group
Age and weight: not specified
Observation period: five days

Evaluation of study quality*

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the time
Study carried out according to OECD guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	No information
Use of vehicle (other than air)	Mixture of equal parts of ethyl alcohol and ether
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution.	Negative
Homogeneity of test atmosphere in breathing zone of animals	A solution of nickel carbonyl was introduced into a syringe, which introduced the solution in a metered air stream. Evaporation was immediate. Air was introduced at one of the upper corners of the chambers and withdrawn at the diametrically opposite corner.
Number of air changes per hour	The number of exact air changes per hour is not stated. The aim was to use an airflow of 550 L/min in the chamber of 539 L, resulting in approximately 60 air changes per hour.
Equilibration time (t95)	Approximately 3 minutes
Start of exposure relative to equilibration	At start of concentration build-up
Actual concentration measurement	Continuous measurement of the concentration of nickel carbonyl present in the chamber was made throughout the 30-minute exposure period. Reference was given to Kincaid *et al*. 1956, who described two colorimetric methods for low and high nickel tetracarbonyl levels.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A
Assessment of Reliability	**C** Study was well performed. Limited to one exposure duration. However; a probit or LC_{50} could not be derived.

* information on the experimental design of the study was obtained from Sunderman *et al*. (1956)

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Mouse	43	NA	30	24/30
	57	NA	30	30/30
	71	NA	30	388/390
	114	NA	30	30/30
	171	NA	30	30/30

Probit function

Deriving a probit function or LC_{50} was not possible for these data.

Study ID: C.2

Author, year: Baselt et al., 1977
Substance: Nickel tetracarbonyl
Species, strain, sex: Rat, albino F344, female
Number/sex/concentration group: 8 to 33 animals/group
Age and weight: 180 g (SD: 16)
Observation period: at least one week

Evaluation of study quality*

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the time
Study carried out according to guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	No information
Use of vehicle (other than air)	Absolute alcohol
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution	No information
Homogeneity of test atmosphere in breathing zone of animals	A solution of 1 to 10% nickel tetracarbonyl in alcohol was introduced into a syringe, which introduced the solution in a metered air stream. The metered air was provided at a predetermined rate. Evaporation was immediately. No information on homogeneity at breathing zone.
Number of air changes per hour	The number of exact air changes per hour is not stated. In a study by the same group (Kincaid *et al*. 1953), the aim was approximately 60 air changes per hour. The volume of the inhalation chamber in this study was 20 liter, corresponding to an air flow of 20 L/min.
Equilibration time (t95)	Approximately 3 min
Start of exposure relative to equilibration	At start of concentration build-up
Actual concentration measurement	Concentrations were analytically measured by gas chromatography. Air was sampled at the center of the chamber by use of a gas-tight syringe.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A

Assessment of Reliability	**C** Study was well performed. Limited to one exposure duration. The study was not given the B1-status as only two (and not three) exposure concentrations in combination with one exposure duration were included.

* information on the experimental design of the study was obtained from Kincaid *et al*. (1953) except for chamber volume and actual concentration measurement.

This study focussed on the antidotal effects of sodium diethyldithiocarbamate, D-penicillamine and triethylenetetramine. The animals were exposed for 15-min via inhalation to tetra nickel carbonyl followed by an i.m. injection with one of the potential antidotes. The results of the control animals are presented here; the control animals received an i.m. injection of sodium chloride.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Rat	1.4×10^3	NA	15	19/26
	1.4×10^3	NA	15	17/26
	1.4×10^3	NA	15	3/8
	4.2×10^3	NA	15	33/33

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Rat	-51.5	7.86	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
15	1333 (C.I. could not be calculated)

No C × t probit function could be calculated from these data alone.

Study ID: C.3

Author, year: Baselt and Hanson, 1982

Substance: Nickel tetracarbonyl
Species, strain, sex: Rat, albino F344, female
Number/sex/concentration group: 8 to 14 animals/group
Age and weight: 180 g
Observation period: one week (it is stated by the author that "animals that died prior to drug treatment were excluded from the experimental groups")

Evaluation of study quality*

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the time
Study carried out according to guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	No information
Use of vehicle (other than air)	Absolute alcohol
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution	No information
Homogeneity of test atmosphere in breathing zone of animals	A solution of 1 to 10% nickel tetracarbonyl in alcohol was introduced into a syringe, which introduced the solution in a metered air stream. The metered air was provided at a predetermined rate. Evaporation was immediately. No information on homogeneity at breathing zone.
Number of air changes per hour	The number of exact air changes per hour is not stated. In a study by the same group (Kincaid *et al*. 1953), the aim was approximately 60 air changes per hour. The volume of the inhalation chamber in this study was 20 liter, corresponding to an air flow of 20 L/min.
Equilibration time (t95)	Approximately 3 min
Start of exposure relative to equilibration	At start of concentration build-up
Actual concentration measurement	Concentrations were analytically measured by gas chromatography. Air was sampled at the center of the chamber by use of a gas-tight syringe.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A

Assessment of Reliability	**C** Study was well performed. Limited to one exposure duration. The study was not given the B1-status as only two (and not three) exposure concentrations in combination with one exposure duration were included.

* information on the experimental design of the study was obtained from Baselt *et al*. 1977. In this paper, reference was made to Kincaid *et al*. (1953) except for chamber volume and actual concentration measurement.

This study focussed on the antidotal effects of disulfiram, sodium diethyldithiocarbamate, D-penicillamine hydrochloride. The animals were exposed for 15-min via inhalation to nickel tetracarbonyl followed by oral dosage of one of the potential antidotes. The results of the control animals are presented here; the control animals received distilled water.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Rat	1.4×10^3	NA	15	6/14
	1.7×10^3	NA	15	7/8

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times lnC$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Rat	-44.8	6.85	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
15	1437 (528-1652)

No C × t probit function could be calculated from these data alone.

Study ID: C.4

Author, year: Kincaid et al. 1953

Substance: Nickel tetracarbonyl
Species, strain, sex: Cat, domestic
Number/sex/concentration group: 1-3/group, sex not specified
Age and weight: Not specified
Observation period: No period specified. After exposure, the experimental animals (specifically described for mice and rats) returned to their cages immediately after exposure, and were allowed to stay there undisturbed until death or complete recovery occurred. It is not stated whether this also applied to the cat study.

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	GLP did not exist at the time
Study carried out according to OECD guideline(s)	OECD guideline 403 did not exist at the time
Stability of test compound in test atmosphere	Experiments independently carried out showed that nickel tetracarbonyl in air at room temperature decomposed by not more than 5% in 50 seconds.
Use of vehicle (other than air)	Absolute alcohol
Whole body / nose-only (incl. head/nose-only) exposure	Whole body
Type of restrainer	N/A
Pressure distribution.	No information
Homogeneity of test atmosphere in breathing zone of animals	A solution of 1 to 10% nickel tetracarbonyl in absolute alcohol was introduced into a syringe, which introduced the solution in a metered air stream. The metered air was provided at a predetermined rate by a pump. Evaporation was immediate. No information on homogeneity at breathing zone.

Number of air changes per hour	The chamber volume as used for cats was initially 45 by 60 by 45 cm (approximately 120 liter). The following is stated by the authors: "The turnover time was approximately 4 minutes. It was first thought that this time was short enough to ensure stability of the nickel tetracarbonyl, but tests later showed that as much as 30% of the material was decomposed on passage through the chamber. Previous exposures in the large chamber were corrected for decomposition, and the volume of the chamber was reduced to eliminate the need for such a correction in future exposures." It is however not clear to which volume the chamber was reduced to. It is not clear whether the same flow of 600-1900 liters per hour, as used for the small chamber, was also applied to the larger chamber.
Equilibration time (t95)	Insufficient information to calculate
Start of exposure relative to equilibration	Not specified
Actual concentration measurement	Nominal concentrations were given based on airflow and injected substance. Nominal concentrations were < 25% saturated vapour concentration. Due to unexpected problems with decomposition of nickel tetracarbonyl, the authors corrected the exposure concentrations for the initial experiments.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A
Assessment of Reliability	**C** Study limited to one exposure duration; no actual concentrations presented, though nominal concentrations calculated. Due to uncertainties related to the exposure and the observation period, the study was given the C-status.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Cat	0.19×10^3	N/A	30	0/1

	0.50 x 10^3	N/A	30	0/1
	1.24 x 10^3	N/A	30	1/1
	1.94 x 10^3	N/A	30	0/2
	2.00 x 10^3	N/A	30	3/3
	2.11 x 10^3	N/A	30	3/3
	2.43 x 10^3	N/A	30	1/1

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Cat	-7.24	1.72	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
30	1207 (C.I. could not be determined)

No C × t probit function could be calculated from these data alone.

Study ID: other C studies

Barnes and Denz (1951) exposed 4 groups of Albino rats (group size 10 to 76 animals) and one group of rabbits (29 animals) to varying concentrations of nickel tetracarbonyl by evaporation, expressed as mg/m^3 x min. Rats were exposed for periods of five to 30 minutes. This resulted in (calculated) concentration-time combinations of 17-23 x 10^3, 29-38 x 10^3, 43-58 x 10^3 and 70 x 10^3 mg/m^3 x min. Mortality percentages in the rat were 65, 77, 84 and 100%, respectively. Rabbits exposed to (calculated) 10-37 x 10^3 mg/m^3 x min resulted in 62% mortality. Animals were observed up to one week after exposure.

In Baselt *et al.* (1977) a preliminary study is described. The description lacks information on experimental design and by whom and when this study was performed. The preliminary study included four exposure groups of 20 rats/group. The animals were exposed to 140, 280, 720 or 1430 mg/m^3 nickel tetracarbonyl for 15 minutes. Mortality ratios after a two week observation period were 5/20, 7/20, 12/20, and 15/20 respectively. The estimated LC_{50} was 580 mg/m^3 with a standard deviation of 90 mg/m^3.

In carcinogenicity assays, Sunderman and Donnelly (1965) reported that 214 of 285 rats died within 3 weeks of a single 30-min inhalation exposure to nickel carbonyl (80 ppm, corresponding to 568 mg/m^3). None of the 19 control rats died during this time period.

Appendix 2 Reference list

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