20240723-nickel hydroxycarbonate-INHOUDELIJK VASTGESTELD

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

Probit function technical support document

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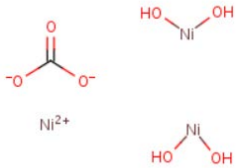
substance name	CAS number
Nickel hydroxycarbonate	**12607-70-4**

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 "inhoudelijk vastgesteld" (approved content).

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

Technical support document nickel hydroxycarbonate



1. Substance identification[1]

CAS-number:	12607-70-4
IUPAC name:	Trinickel monocarbonate tetrahydroxy
Synonyms:	[carbonato(2-)] tetrahydroxytrinickel, nickel(2+) bis(nickeldiol) carbonate, nickel carbonate
Molecular formula:	$Ni_3(OH)_4CO_3$
Molecular weight:	304.1 g/mol
Physical state:	solid (at 20°C and 101.3 kPa)
Boiling point:	No specific information[2]
Vapour pressure:	N/A
Saturated vapor conc:	N/A
Conversion factor:	1 mg/m^3 = 0.079 ppm (at 20°C and 101.3 kPa) 1 ppm = 12.650 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	Human H302, H315, H317, H332, H334, H341, H350i, H360D, H372

2. Mechanism of action and toxicological effects following acute exposure

Acute effects: Data on the acute effects of nickel hydroxycarbonate and its mechanism of action are limited. Acute exposure results in lethality. Health effects or symptoms of high exposure are not clearly identified.
The two available animal studies point towards discoloration of lungs and intestines, irregular/abnormal respiration and hypoactivity, and tremors in some of the animals.
Long-term effects: No information is available on long-term toxicity following acute exposure.

3. Human toxicity data

No informative reports on human toxicity following acute inhalation exposure were identified in which details about both health effects and 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 TSD, ERPG document and EU RAR were not available.
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

[1] Based on ECHA (2023)
[2] ECHA (2023) states that a study does not need to be conducted because the substance is a solid which melts above 300ºC.

- 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 two studies were identified -with two datasets for one species- with data on lethality following acute inhalation exposure. None of the datasets were assigned status A for deriving the human probit function, two datasets were assigned status B and none were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

No studies on sensory irritation were found.

5. Probit functions from individual studies

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

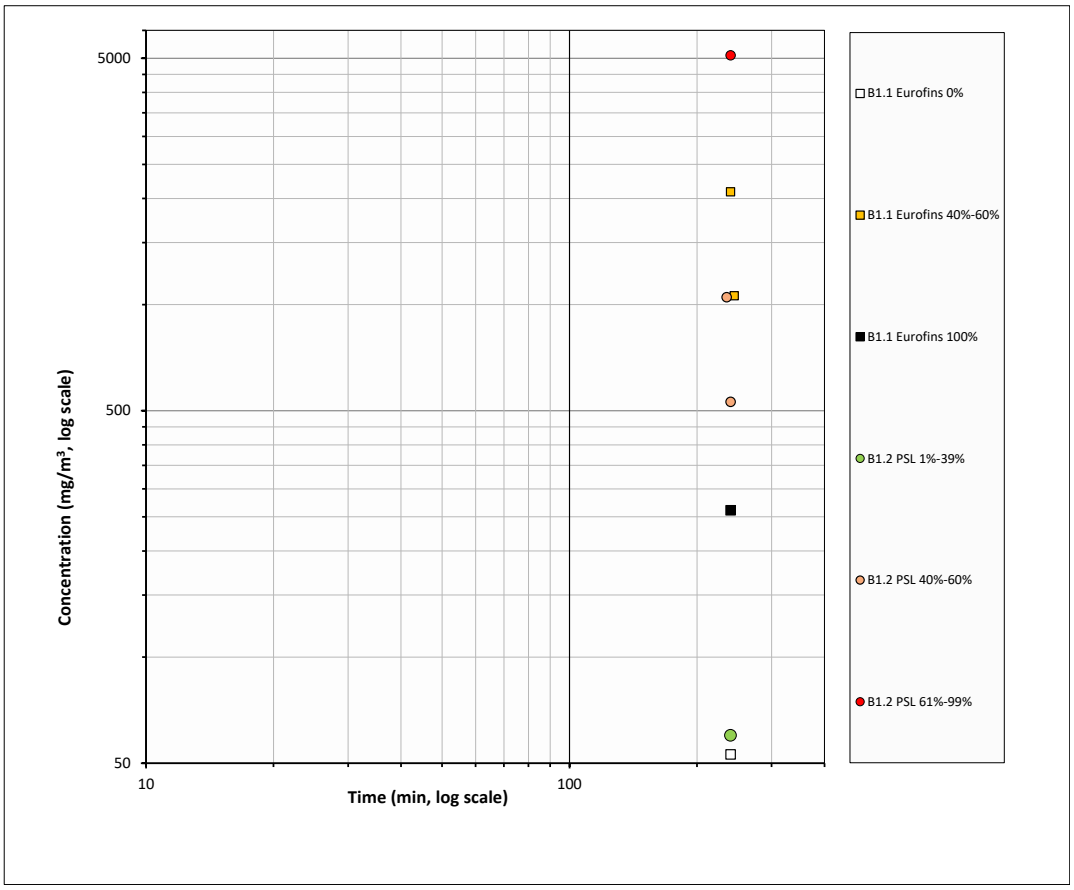


Figure 1 *All available acute lethality data for nickel hydroxycarbonate.*

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

It was not possible to derive a probit function for nickel hydroxycarbonate based on studies with A quality. 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 2.

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

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I. (240-min)	n-value 95% C.I.
B1.1	Rat	*240-min LC_{50}*	479	N/A
B1.2	Rat	*240-min LC_{50}*	827	N/A

The data of studies B1.1 and B1.2 with rats are presented graphically below.

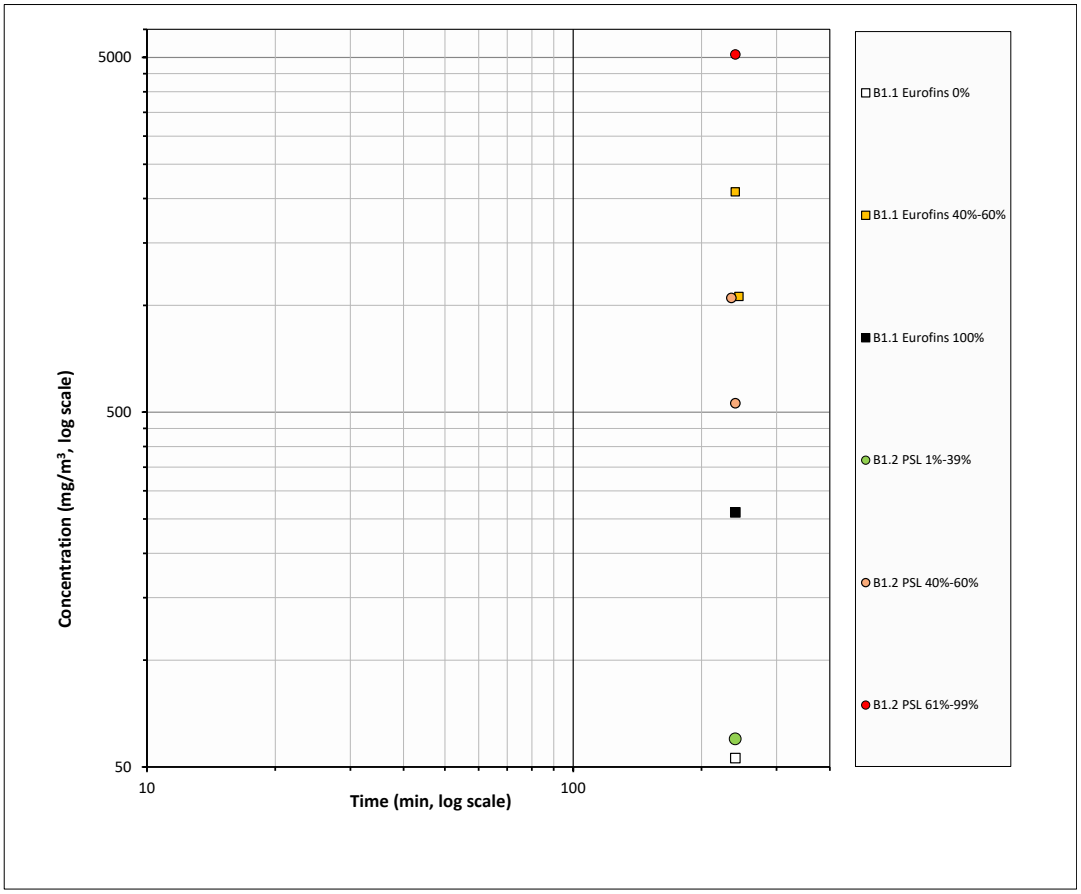


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of nickel hydroxycarbonate (identical to figure 1).*

Based on criteria outlined in the guideline the data from rat studies B1.1 and B1.2 were selected for the final dataset for the derivation of the animal probit function. These rat studies were the only available studies with B1 quality; studies with A quality were not available. The data that were selected for final analysis of the animal probit function are presented in Table 2 and Figure 3.

The final data eligible for calculating the animal probit function contains two datasets from two studies and includes data from one animal species.

Table 2 *Data selected for the derivation of the animal probit function of nickel hydroxycarbonate (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. (240-min)	n-value 95% C.I.
B1.1	Rat	*240-min LC_{50}*	479	N/A
B1.2	Rat	*240-min LC_{50}*	827	N/A

The data of the selected datasets are presented graphically below.

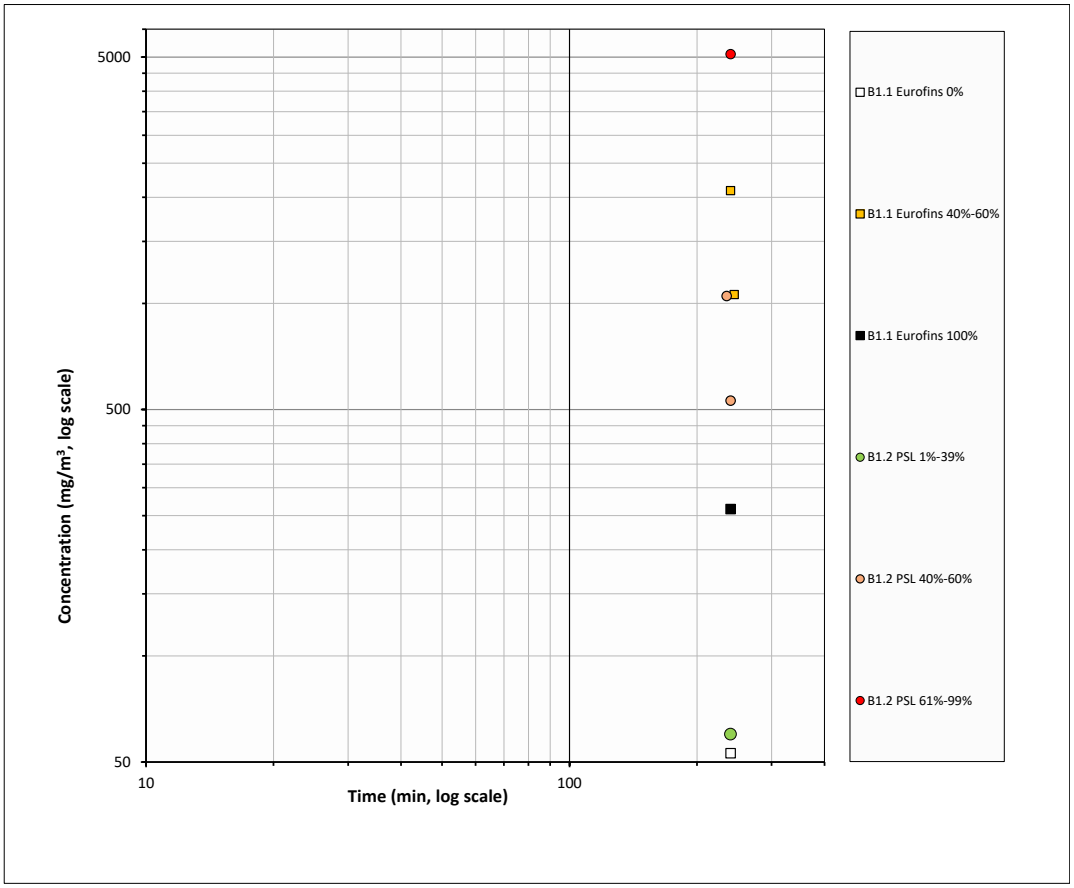


Figure 3 *Final data selected for derivation of the animal probit function of nickel hydroxycarbonate (identical to figures 1 and 2).*

6. Derivation of the human probit function

To derive the human probit function, the results from rat studies B1.1 (Eurofins, 2010) and B1.2 (PSL, 2021) have been used to derive a point of departure as outlined above. These studies are well-performed but are limited to one exposure duration. Therefore, the B1-status was assigned to both studies.

However, apparent inconsistent results were obtained from these studies. Clear differences in lethality ratios and corresponding LC_{50} values were noted between male and female animals, with higher lethality in male animals for study B1.1 and lower lethality in male animals for study B1.2. Based on the results of study B1.1, 240-min LC_{50} values of 244 mg/m^3 (males), >2090 mg/m^3 (females), 479 mg/m^3 (sexes combined) were derived, whereas for study B1.2 240-min LC_{50} values of 3020 mg/m^3 (males), 214 mg/m^3 (females), 827 mg/m^3 (sexes combined) were obtained.

Some other issues were noted. Study B1.1 included only a single female exposure group thereby not allowing to establish an LC_{50} value for female animals.
Based on the results of this highest concentration group (i.e. 2090 mg/m^3) in the B1.1 study, viz. 1/5 mortality in females and 4/5 in males, next only five males (and no other females) were tested at the three lower concentration levels. It could be argued that the single female datapoint of study B1.1 should therefore be disregarded and solely the male data of study B1.1 should be used to calculate the animal probit function and corresponding 240-min LC_{50} value. Further, no clear concentration-response curve could be derived, especially when considering the male data of study B1.1. This also creates uncertainty on the use of this study for human probit function derivation.
According to the REACH registration dossier, the study of PSL (2021) was conducted "*due to some concerns regarding the Eurofins (2010) study, including the possibility of a gender-specific effect, females tested at only one dose, and male data did not fit a strong dose-response curve*". Nevertheless, in the REACH registration dossier, the most conservative 240-min LC_{50} values in both acute inhalation studies (i.e. 240 mg/m^3 for male rats (Eurofins, 2010) and 263 mg/m^3 for female rats (PSL, 2021)) were selected as a conservative approach for classification purposes (ECHA, 2023).
The Expert Panel on Probit Functions considers that no well-substantiated explanation could be found for the difference in response between male and female animals in both studies, or for the absence of a clear concentration-response. Both studies have comparable study design (and were performed in the same laboratory with a 11-year time interval), and no biological explanation can be found that could explain the observations. Further, the test substance, being a powder, was expected to be stable for the duration of testing according to the study authors of study B1.1. Based on this, it is not expected that stability might be an issue for study B1.2 which was performed in the same laboratory as study B1.1.
Overall, disregarding one of the sexes or one of the studies is not considered justified. The results of these studies B1.1 and B1.2 have therefore been used for human probit derivation, with analysis of sexes combined. It is however acknowledged that this introduces some uncertainty which supports applying an assessment factor for adequacy of the database (see table 3 below).

First, the default n-value of 2 was selected as no experimentally derived value for n was available.

Second, the LC_{50}-values of all applicable B1-studies were calculated for a common exposure duration of 240 minutes.

Finally, the rat-specific geometric mean LC_{50}-value was calculated from all available (time-scaled) LC_{50} values of studies B1.1 and B1.2. The species-specific 240-min LC_{50}-value was 629 mg/m^3 for the rat. The formula for the geometric mean of time-scaled LC_{50}-values from 1 species is as follows:

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

With $\overline{LC_{50}}$ = geometric mean LC_{50}-value
$LC_{50,i}$ = LC_{50}-value of study i.
m = number of observations on LC_{50}-values (i=1…m).

The Point of Departure for the human probit function is a 240-minute geometric mean animal LC_{50} value of 629 mg/m^3 and the default n-value of 2.

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	Studies with analytically determined concentrations available
Adequacy of database:	2	Though two well-performed B1 studies were available, conflicting results were obtained between the response of male and female animals in the B1 studies which introduces some uncertainty.

The estimated human equivalent 240-minute LC_{50} value is 629 / 6 = **105 mg/m³**.

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**.

The human probit function is then calculated on the human equivalent 240 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1 \times \ln(105^2 \times 240)$ resulting in the a-value of **-9.79**.

$Pr = -9.79 + 1 \times \ln(C^2 \times t)$ with C in mg/m³ and t in min.

The derived human probit function has a scientifically acceptable basis. The probit function is based on 2 studies in the rat with B1 quality, with 105 animals, a single exposure duration, and response rates ranging 0% to 100%.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 45 mg/m³ and the calculated human 60 min LC_1 (Pr = 2.67) is 66 mg/m³.

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

Estimated level	30 min (mg/m³)	60 min (mg/m³)
0.1% lethality, this probit	63	45
1% lethality, this probit	93	66
AEGL-3	-	-
ERPG-3	-	-
LBW	-	-

Equivalent (inter)national guideline levels are not available.

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: ***Eurofins (2010)***
Substance: nickel hydroxycarbonate
Species, strain, sex: rat, Sprague-Dawley, male/female
Number/sex/conc. group: 5 males per concentration group, 5 females only for the highest concentration group
Age and weight: 8-10 week, males 275-356 grams, females 204-242 grams.
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*Yes*
Study carried out according to OECD 403 guideline(s)	*Yes*
Stability of test compound in test atmosphere	*Test substance was expected to be stable for the duration of testing according to the study authors (though no data or justification were provided)*
Use of vehicle (other than air)	*N/A*
Whole body / nose-only (incl. head/nose-only) exposure	*Nose-only*
Type of restrainer	*Polycarbonate holding tubes which seal to the chamber with an "O" ring during exposure. The base unit terminates the chamber with a 0.5-inch diameter tube for discharged air.*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*The test substance was aerosolized, without additional grinding. Filtered air was supplied by an air compressor to the dust generator. Generated aerosolized dust was then fed into the chamber. Compressed air was introduced into the chamber to help uniformly distribute the test atmosphere by creating a vortex at the chamber inlet.*
Number of air changes per hour	*284 air changes per hour using a nose-only inhalation chamber with an internal volume of 6.7 L, corresponding to an air flow of 32 L/min.*
Equilibration time (t95)	*Insufficient information to calculate t95.* *The study authors presented a t90 of 0.5 min and t99 of 1 min.*

Start of exposure relative to equilibration	*At each level, the exposure period was extended beyond 4 hours to allow the chamber to reach equilibrium (t99). At the end of each exposure period, the generation was terminated and the chamber was operated for a further 15 minutes with clean air. Excess test substance was removed from the fur of each animal.*
Actual concentration measurement	*Gravimetric samples were withdrawn at five or six intervals from the breathing zone of the animals during each exposure. Samples were collected using 25 mm glass fibre filters in a filter holder attached by ¼-inch tygon tubing to a vacuum pump. Filter papers were weighed before and after collection to determine the mass collected. This value was divided by the total volume of air sampled to determine the chamber concentration. Sample airflows were measured using a Mass Flowmeter*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*MMAD: 2.1, 2.5, 2.4 and 3.05 µm for concentrations of 53, 261, 1060, and 2090 mg/m³, respectively, based on graphic analysis of the particle size distribution (using two-cycle logarithmic probit axes). Determined using an eight-stage Andersen cascade impactor. No GSD mentioned.*
Assessment of Reliability	***B1*** *Well-performed study, limited to one exposure duration.*

Results

Species	Concentration (mg/m³)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
Rat	53		240	0/5	-*
Rat	261		240	5/5	-*
Rat	1060		240	3/5	-*
Rat	2090		240	4/5	1/5

* according to the study authors: based on the results of the 2090 mg/m³ exposure level, only five males were tested at the 53, 261 and 1060 mg/m³ levels.

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/m³, t for time in minutes.

Probit function	Species	a	b	n-value
Male data only	Rat	2.28	0.495	N/A

Sexes combined	Rat	3.61	0.226	N/A

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Male	LC_{50} (mg/m^3) 95%-C.I. Female	LC_{50} (mg/m^3) 95%-C.I. Combined
240	244 (Large variances disable estimating 95% confidence-limits)	The data do not allow calculating an LC_{50} (single concentration group tested); 240 min LC_{50} estimated to be >2090 mg/m^3	479 (Large variances disable estimating 95% confidence-limits)

The study author Eurofins (2010) estimated the following:

- Females: 4 hour LC_{50} > 2090 mg/m^3 (the data do not permit calculation of the LC_{50} for females)
- Males: 4-hour LC_{50}: 243.7 mg/m^3 (95%-C.I.: 1.2 – 49700 mg/m^3)

Results per sex showed a difference between the LC_{50}-values for the males and females with a factor of more than 2. However, the sex difference observed in the study cannot be explained by physiological differences in male and female animals. The data from both sexes, therefore, were pooled and analysed to derive the animal probit function.

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

Study ID: B1.2

Author, year: ***Product safety Labs (2021)***
Substance: nickel hydroxycarbonate
Species, strain, sex: rat, Sprague-Dawley, albino, male/female
Number/sex/conc. Group: 10/sex/conc.
Age and weight: 8-9 week, males 227.9-311.8 grams, females 165.0-227.4 grams
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*Yes*
Study carried out according to OECD 403 guideline(s)	*Yes*
Stability of test compound in test atmosphere	*Not determined as part of this study.*
Use of vehicle (other than air)	*N/A*
Whole body / nose-only (incl. head/nose-only) exposure	*Nose-only*
Type of restrainer	*Polycarbonate holding tubes which seal to the chamber with an "O" ring during exposure. The base unit terminates the chamber with a 0.5-inch diameter tube for discharged air.*
Pressure distribution	*The exposure was conducted under slight negative pressure.*
Homogeneity of test atmosphere in breathing zone of animals	*The test substance was aerosolized, without additional grinding. Filtered air was supplied by an air compressor to the dust generator. Generated aerosolized dust was then fed into the chamber. Compressed air was introduced into the chamber to help uniformly distribute the test atmosphere by creating a vortex at the chamber inlet.*
Number of air changes per hour	*77 air changes per hour using a nose-only inhalation chamber with an internal volume of 28 L, corresponding to an air flow of 36 L/min.*
Equilibration time (t95)	*Insufficient information to calculate t95.* *The study authors presented a t90 of 1.79 min and t99 of 3.58 min.*
Start of exposure relative to equilibration	*At each level, the exposure period was extended beyond 4 hours to allow the chamber to reach equilibrium (t99). At the end of each exposure period, the generation was terminated and the chamber was operated for a further 15 minutes with clean air. Excess test substance was removed from the fur of each animal.*

Actual concentration measurement	*Gravimetric samples were withdrawn at six intervals from the breathing zone of the animals during each exposure. Samples were collected using 37 mm glass fibre filters in a filter holder attached by ¼-inch Tygon tubing to a vacuum pump. Filter papers were weighed before and after collection to determine the mass collected. This value was divided by the volume of air sampled to determine the chamber concentration.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*MMAD of 2.64, 2.16, 2.48 and 2.76 µm and GSD of 2.46, 2.31, 2.32, 2.38 for concentrations of 60, 530, 1050, and 5100 mg/m³, respectively, based on graphic analysis of the particle size distribution (using two-cycle logarithmic probit axes). Determined using an eight-stage Andersen ambient particle sizing sampler.*
Assessment of Reliability	***B1*** *Well-performed study, limited to one exposure duration.*

Results

Species	Concentration (mg/m³)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
Rat	60		240	1/10	3/10
Rat	530		240	3/10	7/10
Rat	1050		240	5/10	5/10
Rat	5100		240	4/10	10/10

Probit function

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

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

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

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	3.20	0.34	-0.89	N/A
Sexes combined	Rat	2.98	0.30		N/A

Duration (min.)	LC_{50} (mg/m³) 95%-C.I. Male	LC_{50} (mg/m³) 95%-C.I. Female	LC_{50} (mg/m³) 95%-C.I. Combined
240	3020 (853.6 - 39420)	214.2 (22.54 – 753.8)	827 (Large variances disable estimating 95% confidence-limits)

The study author Product Safety Lab (2021) estimated the following:

- Females: 4 hour LC_{50}: 262.7 mg/m^3 (34.4 – 716.7 mg/m^3)
- Males: 4 hour LC_{50}: 5213 mg/m^3 (95%-C.I.: 315.4 – 86166 mg/m^3)
- Combined: 4 hour LC50: 827.0 mg/m^3 (95%-C.I.: 269.5 – 3192.5 mg/m^3)

Results per sex showed a difference between the LC_{50}-values for the males and females with a factor of more than 2. However, the sex difference observed in the study cannot be explained by physiological differences in male and female animals. The data from both sexes, therefore, were pooled and analysed to derive the animal probit function.

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

Appendix 2 Reference list

ECHA (2023). REACH registration dossier [carbonato(2-)]tetrahydroxynickel. First published 20 December 2010, last modified 17 April 2023. https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/15292/

Eurofins (2010). Nickel hydroxycarbonate. Acute inhalation toxicity study in rats – defines LC_{50}. Eurofins Product Safety Laboratories, Daytona, New Jersey, 10 March 2010.

Product Safety Labs (2021). Nickel hydroxycarbonate. Acute inhalation toxicity in rats with a 14-day observation period. Products Safety Labs, Daytona, New Jersey, 13 October 2021.

Ruijten M.W.M.M., J.H.E. Arts, P.J. Boogaard *et al*. Methods for the derivation of probit functions to predict acute lethality following inhalation of toxic substances. RIVM report 2015-0102. Bilthoven, RIVM, 2015.