KEMI
Swedish Chemicals Agency

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Methacrylamide

EC No 201-202-3

CAS RN 79-39-0

Evaluating Member State: Sweden

Dated: 23 June 2022

Evaluating Member State Competent Authority

Swedish Chemicals Agency
Box 2
SE-172 13 Sundbyberg
Tel: +468-519 41 100
Fax: +468-735 76 98
Email: kemi@kemi.se
Website: http://www.kemi.se/en

Year of evaluation in CoRAP: 2016

Before concluding the substance evaluation a Decision to request further information was issued on: 28 May 2018.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The Substance methacrylamide (EC No 201-202-3; CAS RN 79-39-0) (hereafter 'the Substance') was originally selected for substance evaluation to clarify concerns about:

- human health-neurotoxic potential

- exposure of workers

During the evaluation an additional concern was identified:

- derivation of the DNELs

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

In 2010, a compliance check decision (CCH-D-0000000719-67-05/F) was sent to the registrant(s) requesting information related to exposure assessment and physico-chemical properties. The registrant(s) submitted an updated dossier in response to the decision.

In 2018, another compliance check decision (CCH-D-2114394755-33-01/F) was sent to the registrant(s) requesting a Prenatal developmental toxicity study (OECD TG 414). This information was not provided by the deadline of 8 March 2021.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the Substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	✓

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Not applicable.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	
Actions by the registrants to ensure safety, as reflected in the registration dossiers(e.g. change in supported uses, applied risk management measures, etc.)	
Currently, no regulatory follow-up is foreseen at EU-level, However, conclusion on possible regulatory follow-up awaits the results of the compliance check.	X

A Developmental neurotoxicity (DNT) study, according to OECD TG 426 was requested in the SEv decision[2] and provided by the registrant(s).

The data confirmed the Substance is a developmental neurotoxicant. However, the eMSCA concludes that the observed developmental neurotoxicity effects may not meet the criteria for classification of the substance as Repr. Category 1B for developmental toxicity.

5.2. Other actions

Not applicable.

[2] 71bbf2ea-27c9-06e3-7b75-0494192c9cbd (europa.eu)

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Table 3

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
RMOA	2023	SE

The eMSCA may perform a RMOA once the information requested in the CCH decision sent to the registrant(s) in 2018, concerning prenatal developmental toxicity is available. The final report from the study is expected in the first quarter of 2023.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance was originally selected for substance evaluation to clarify concerns about:

- human health-neurotoxic potential

- exposure of workers

During the evaluation an additional concern was identified:

- derivation of the DNELs

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Neurotoxic potential	**Concern confirmed.** A developmental neurotoxicity study requested under SEv confirmed that the substance causes toxicity to the developing nervous system. No further action under SEv.
Exposure of workers	**Concern confirmed.** No further action under SEv.
Derivation of the DNELs	**Concern refuted** The CSR(s) were updated with information on DNEL derivation. Also, the registrants provided new risk assessments based on the estimated exposures. No further action under SEv.
Additional endpoints	
Toxicokinetics	Methacrylamide /metabolites were systemically available after dermal/intravenous application.
Acute toxicity	eMSCA supports registrant(s) conclusion to self-classify methacrylamide as Acute Tox. 4 H302: Harmful if swallowed.
Corrosion/irritation	eMSCA supports the registrant(s) self-classification of methacrylamide as Eye Irrit. 2 H319: Causes serious eye irritation, and no classification for skin irritation.
Sensitisation	eMSCA supports the registrant(s) conclusion that methacrylamide is not a skin sensitiser.
Repeated dose toxicity	eMSCAS supports the registrant(s)self-classification of methacrylamide as STOT SE 2 (H371) and STOT RE 2 (H373) for effects on the nervous system, and as STOT SE 3 (H335) for effects on the respiratory tract.
Mutagenicity	All results were negative in the *in vitro* studies in bacteria and mammalian cells and negative in *in vivo* studies. The eMSCA agrees with the registrant(s) conclusion that methacrylamide is not mutagenic.

Carcinogenicity	Methacrylamide is equivocally carcinogenic in studies with low reliability. The eMSCA cannot conclude on carcinogenicity of methacrylamide.
Reprotoxicity	The available reproductive toxicity studies show that methacrylamide causes adverse effect on development, specifically developmental neurotoxicity, caused by pre and/or postnatal exposure to developing animals. Developmental neurotoxicity of methacrylamide is manifested as both functional and structural effects on the nervous system of the offspring early in life and during adulthood.

7.2. Procedure

The Substance was included in the Community Rolling Action Plan (CoRAP) for substance evaluation in 2016 by the competent authority of Sweden. The scope of the evaluation was human health, targeted to the concern for neurotoxicity.

In April 2017, a substance evaluation (SEv) draft decision was sent to the registrant(s) for comments. The registrant(s) provided comments to the draft decision. In May 2018, a final SEv decision was sent to the registrant(s) with a request for a developmental neurotoxicity study, according to the OECD TG 426. Also, in this decision further information on derivation of DNELs for the long-term dermal systemic effects was requested.

In May 2018, a compliance check (CCH) decision requesting a prenatal developmental toxicity study, according to the OECD TG 414, was sent to the registrant(s).

In 2021, the registration(s) were updated with the information requested in the SEv decision. The eMSCA evaluated the new information and concluded that no further information request under SEv was needed.

In January 2022, the eMSCA concluded the SEv. The eMSCA plans to perform a RMOA for the Substance to identify if further risk management measures are needed, based on all the available information including the OECD TG 414 study requested under CCH.

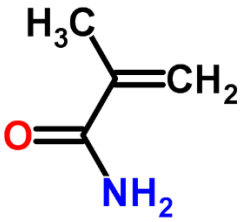
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Methacrylamide
EC number:	201-202-3
CAS number:	79-39-0
Index number in Annex VI of the CLP Regulation:	NA
Molecular formula:	C_4H_7NO
Molecular weight range:	85.1045
Synonyms:	2-Methyl-2-propenamide, 2-Methyl-acrylamide, Methacrylic acid amide, Methacrylic amide

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 6

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	solid
Vapour pressure	0.0015 hPa at 20 °C
Water solubility	100 g/L at 25 °C
Partition coefficient n-octanol/water (Log Pow)	-0.15 at 25 °C
Particle size distribution	D90: 1644 µm D50: 967 µm D10: 348 µm D1.15: 47.94 µm
Melting point	110-111°C

7.5. Manufacture and uses

7.5.1. Quantities

Table 7

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☒ 10 – 100 t	☒ 100 – 1000 t	☒ 1000- 10,000 t	☒ 10,000-50,000 t
☒ 50,000 – 100,000 t	☒ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☒ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 8

USES	
	Use(s)
Uses as intermediate	Use as intermediate in synthesis of derivatives at industrial site.
Formulation	In formulation (mixture) and repacking of preparations.
Uses at industrial sites	In emulsion polymerisation, synthesis of derivatives, silk weighting and reactive resins.
Uses by professional workers	In reactive resins.
Consumer Uses	No consumer use identified.
Article service life	No article service life identified.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonised classification available.

7.6.2. Self-classification

- In the registration(s)*:*

Acute Tox. 4	H302: Harmful if swallowed
Eye Irrit. 2	H319: Causes serious eye irritation
STOT SE 3	H335: May cause respiratory irritation
STOT SE 2	H371: May cause damage to nervous system
STOT RE 2	H373: May cause damage to nervous system through prolonged or repeated exposure

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory[3]*:*

Skin Irrit. 2	H315: Causes skin irritation
Acute Tox. 4	H332: Harmful if inhaled
Carc. 1B	H350: May cause cancer (1 notifier out of total 797)
Repr. 2	H361: Suspected of damaging fertility or the unborn child (1 notifier out of total 797)

7.7. Environmental fate properties

Not relevant for this evaluation.

[3] Last accessed in March 2022.

7.8. Environmental hazard assessment

Not relevant for this evaluation.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

One key *in vivo* study (Exp Key Basic toxicokinetics.004) examining the absorption, distribution and excretion of the Substance when administered dermally to rabbits, rats and mice, and through I.V injection to rabbits; and one supporting *in vitro* metabolism study (Exp Supporting Basic toxicokinetics.005) are reported in the registration dossier(s). Two other studies on metabolism as well as one other study on distribution are also reported (NS Basic toxicokinetics.001, NS Basic toxicokinetics.002, Exp NS Basic toxicokinetics.003). In the key *in vivo* study, 24 hours after dermal application of [^{14}C]methacrylamide to rabbits, the majority of the radioactivity remained at the application site with an accumulation in the hair follicles and 23 – 52% was excreted in the urine. The radioactivity was fairly evenly distributed among tissues, with the exception of a higher concentration in the liver. Twenty-four hours after dermal application of [^{14}C]methacrylamide to rats only 3.7 – 5.7% of the radioactivity was excreted in the urine. Twenty-four hours after I.V. injection, the radioactivity was highest in liver; followed by serum, kidney and total blood. Lower levels were found in brain, sciatic nerve and muscle. Eighty-six percent of the radioactivity was excreted in the urine after 24 hours of I.V. injection. Other studies on metabolism were not able to identify any metabolites but a cytochrome P-450 dependent metabolism of the Substance was suggested in the *in vitro* study (Exp Supporting Basic toxicokinetics.005).

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity: oral

A GLP compliant acute oral toxicity study with reliability 1 (reliable without restrictions) in accordance with OECD TG 401 (Acute Oral Toxicity) is reported as a key study (Exp Key Acute toxicity: oral.011). Wistar rats of both sexes were given a single dose of the Substance by gavage at dose levels 1000, 2000 and 3000 mg/kg bw. Sedation was observed in both sexes at all dose levels. Ataxia, ventral body position and curved body position were observed in both sexes at 2000 mg/kg and higher. Mortality was observed at 2000 mg/kg and higher. The LD50 values were 1938 mg/kg for males and 1653 mg/kg for females, with a combined LD50 of 1818 mg/kg.

Another GLP compliant acute oral toxicity study with reliability 1 (reliable without restrictions) in accordance with OECD TG 401 (Acute Oral Toxicity) is reported as a supporting study (Exp Supporting Acute toxicity: oral.001, Exp Supporting Acute toxicity: oral.003). Crj: CD(SD) rats of both sexes were given orally a single dose of the Substance at dose levels 0, 1315, 1512, 1739 and 2000 mg/kg bw. Tremor, slight necrosis of neurocyte in cerebellar nuclei and decreased body weight were observed in both sexes at 1315 mg/kg and higher. Staggering gait, salivation, irritability, soiled perioral fur, sitting position and orange yellow urine was observed in both sexes at 1512 mg/kg and higher. In males, slight vaculoar degeneration in molecular layer, slight degeneration of sciatic nerve fibers, moderate necrosis of neurocyte and slight gliosis in hippocampus and slight necrosis of neurocyte in amigdala nuclei were seen at 1512 mg/kg; and slight necrosis in Purkinje cells and small testes were seen at 1512 and 1739 mg/kg. In females, slight necrosis in Purkinje cells and slight degeneration of sciatic nerve fibers were seen at 1739 mg/kg. Slight atrophy of the spleen was observed at 1512 mg/kg and higher in females, and at 2000 mg/kg in males. Histopathological changes of the testes and epididymis were seen in males at 1512 mg/kg and higher. Mortality was observed at 1512 mg/kg and higher. The LD50 values were 1789 mg/kg for males and 1774 mg/kg for females.

In addition to the key and supporting studies, 15 other studies are also reported in the registration dossier(s). They are briefly summarised in table 9 below. Further information on the studies can be found on the ECHA dissemination webpages.

Table 9: Summary of the oral acute toxicity studies reported in the registration dossier(s)

Reference	Reliability/ guideline *Deviations from the guideline if any*	Test material *Species/strain/Sex*	No./sex/dose Route	Doses	Results	Effect Level
Exp Key Acute toxicity: oral.011	1/OECD TG 401 (Acute Oral Toxicity)	Methacrylamide, 90% *Rat/Wistar/M&F*	5 Oral: gavage	1000, 2000, 3000 mg/kg	1000 mg/kg: Sedation, ruffled fur (females). Dark red mottled lung. All animals survived. 2000 mg/kg: Sedation, ataxia, ventral body position, curved body position. Ruffled fur and lacrimation (females). Dark-read mottled, dark-red discoloured and reddish discoloured lungs. Meteorism, enlarged small testines and yellowish contents in stomach. 2 males and 4 females died within 24 hours. 3000 mg/kg: Sedation, ataxia, ventral body postion, latera-abdominal position, curved body position. Ruffled fur and lacrimation (females). The surviving rat had recovered within 2 to 14 days. Dark-read discoloured, dark red to black discoloured and dark-red mottled lungs. Light mottled liver. Severe meteorism in ventral stomach. Red to yellowish contents of intestines. All animals died within 5 hours.	LD50 (males): 1938 mg/kg bw LD50 (females): 1653 mg/kg bw LD50 (combined): 1818 mg/kg bw
Exp Supporting Acute toxicity: oral.001	1/OECD TG 401 (Acute Oral Toxicity)	Methacrylamide, 99.5% *Rat/Crj: CD(SD) /F*	5 Oral	0, 1315, 1512, 1739, 2000 mg/kg	1739 mg/kg: Slight necrosis in purkinje's cells, slight degeneration of sciatic nerve fibers. 1512 mg/kg or more: Staggering gait, salivation, irritability, soiled perioral fur, sitting position, orange yellow urine. Slight atrophy of spleen. 1315 mg/kg or more: Tremor and decrease in body weight. Slight necrosis of neurocyte in cerebellar nuclei.	LD50: 1774 mg/kg bw
Exp Supporting Acute toxicity: oral.003	1/OECD TG 401 (Acute Oral Toxicity)	Methacrylamide, 99.5% *Rat/Crj: CD(SD) /M*	5 Oral	0, 1315, 1512, 1739, 2000 mg/kg	2000 mg/kg: Slight atrophy of spleen. 1739 mg/kg or more: Intracelial cell fragment in epididymis. 1512 mg/kg or more: Staggering gait, salivation, irritability, soiled perioral fur, sitting position, orange yellow urine. Moderate degeneration or necrosis of Step1 spermatid, slight multinuclear giant cell in seminiferous tubule, moderate decrease of elongate spermatid and slight or moderate decrease of pachytene spermatocyte at	LD50: 1789 mg/kg bw

Reference	Reliability/ guideline *Deviations from the guideline if any*	Test material *Species/strain/Sex*	No./sex/dose Route	Doses	Results	Effect Level
					stage VII-XII in testes, decrease of spermatoza in epididymis. 1315 mg/kg or more: Tremor and decrease in body weight. Slight necrosis of neurocyte in cerebellar nuclei. In addition, slight vacuolar degeneration in molecular layer, slight degeneration of sciatic nerve fibres, moderate necrosis of neurocyte and slight gliosis in hippocampus and slight necrosis of neurocyte in amygdala nuclei were seen at 1512 mg/kg; and slight necrosis in purkinje's cells and small testes were seen at 1512 and 1739 mg/kg.	
Exp NS Acute toxicity: oral.009	2/non-guideline study *Range-finding test*	Methacrylamide *Rat/NMRI/NS*	2 Oral: gavage	250, 500, 1000, 2500 mg/kg bw	No deaths occurred up to 500 mg. All animals died within 24 hours at 1000 and 2500 mg/kg.	LD100: 1000-2500 mg/kg bw
NS Acute toxicity: oral.017	2/non-guideline study *LD50 according to Weil (1952)*	Methacrylamide, >95% *Mouse/ddY/M*	4 Oral: gavage	Not specified	-	LD50: 451 mg/kg bw
Exp NS Acute toxicity: oral.012	2/non-guideline study *No data*	Methacrylamide *Rat/NS/NS*	- Oral	Not specified	-	LD50: 1380-1950 mg/kg bw
Exp NS Acute toxicity: oral.014	2/non-guideline study *No data*	Methacrylamide *Rat/NS/NS*	- Oral	Not specified	-	ALD50: ca 1500 mg/kg bw
Exp NS Acute toxicity: oral.010	2/non-guideline study *No data*	Methacrylamide *Rabbit/NS/NS*	- Oral: gavage	Not specified	-	ALD50: 500-1000 mg/kg bw
Exp NS Acute toxicity:	2/non-guideline study	Methacrylamide	- Oral:	Not specified	-	ALD50: 100-1000 mg/kg

Reference	Reliability/ guideline *Deviations from the guideline if any*	Test material *Species/strain/Sex*	No./sex/dose Route	Doses	Results	Effect Level
oral.007	*No data*	*Cat/NS/NS*	gavage			bw
Exp NS Acute toxicity: oral.006	4/non-guideline study *Standard acute screening toxicity study, post-administration period: 10 to 11 days*	Methacrylamide *Rat/NS/M*	1 Oral: gavage	130, 670, 1000, 1500, 2250, 3400, 5000 mg/kg bw	1500 mg/kg and below: No rats found dead. Rats initially lost weight and then began to gain weight. 2250 mg/kg and higher: Discomfort, weakness, marked salivation. All rats were dead within 11 days. 5000 mg/kg: Incoordination, dragging self around.	LD100: 2250 mg/kg bw LDLo: 1500 mg/kg bw
Exp NS Acute toxicity: oral.005	4/non-guideline study *No data*	Methacrylamide *Dog/NS/NS*	2 Oral	Not specified	-	LD50: 500 mg/kg bw
NS NS Acute toxicity: oral.018	4/non-guideline study *No data*	Methacrylamide *Rat/NS/NS*	- Oral	Not specified	-	LD50: 1223 mg/kg bw
Exp NS Acute toxicity: oral.004	4/non-guideline study *No data*	Methacrylamide *Rat/NS/NS*	- Oral	Not specified	-	LD50: 1538 mg/kg bw
NS NS Acute toxicity: oral.008	4/non-guideline study *No data*	Methacrylamide *Rat/NS/NS*	- Oral	Not specified	-	LD50: 1750 mg/kg bw
NS NS Acute toxicity: oral.013	4/non-guideline study *No data*	Methacrylamide *Mouse/NS/NS*	- Oral	Not specified	-	LD50: 475 mg/kg bw
Exp NS Acute toxicity: oral.015	4/non-guideline study *No data*	Methacrylamide *Mouse/NS/NS*	- Oral	Not specified	-	LD50: 567 mg/kg bw

Reference	Reliability/ guideline *Deviations from the guideline if any*	Test material *Species/strain/Sex*	No./sex/dose Route	Doses	Results	Effect Level
NS NS Acute toxicity: oral.016	4/non-guideline study *No data*	Methacrylamide *Rabbit/NS/NS*	- Oral	Not specified	-	LD50: 1865 mg/kg bw
Exp NS Acute toxicity: oral.002	4/non-guideline study *No data*	Methacrylamide *Rat/NS/NS*	- Oral	Not specified	-	Threshold for acute nervous system effects: 200 mg/kg bw

Acute toxicity: inhalation

In a GLP compliant 14-day range finding study (Exp NS Acute toxicity: inhalation.004) with reliability 2 (reliable with restrictions) male rats of Sprague-Dawley strain were exposed to concentrations of 0.030, 12.8, 62.6 and 286 mg/m^3 for 6 hours/day, 7 days/week for 2 weeks. No mortality or signs of neurotoxicity were seen at any of the dose levels. Histopathological examination revealed central lobular hepatocellular hypertrophy in the liver and squamous/squamoid metaplasia of the columnar epithelium covering the central seromucous gland in the larynx at 62.6 and 286 mg/m^3.

Four other studies reported in the registration dossier(s) are briefly summarised in table 10 below. Further information on the studies can be found on the ECHA dissemination webpages.

Table 10: Summary of the inhalation acute toxicity studies reported in the registration dossier(s)

Reference	Reliability/ guideline *Deviations from the guideline if any*	Test material *Species/strain/Sex*	No./sex/dose Route *Duration*	Doses	Results	Effect Level
Exp NS Acute toxicity: inhalation.004	2/non-guideline study *14-day Range-finding study for a 28-day subacute inhalation study. Methacrylamide was*	Methacrylamide *Rat/Sprague-Dawley/M*	5 Inhalation: nose only *14 days*	0.030, 12.8, 62.6, 286 mg/m^3	No mortality or signs of neurotoxicity at any of the dose levels. Histopathological changes in the liver and larynx at mid and high dose levels.	LCLo: 286 mg/m^3

Reference	Reliability/ guideline *Deviations from the guideline if any*	Test material *Species/strain/Sex*	No./sex/dose Route *Duration*	Doses	Results	Effect Level
	administered via nose only for 6 hours/day, 7 days/week, for 2 weeks.					
Exp NS Acute toxicity: inhalation.001	2/non-guideline study *No data*	Methacrylamide *Rat/NS/NS*	12 in total Inhalation *8 hours*	Not specified	No toxicity observed.	-
Exp NS Acute toxicity: inhalation.006	3/non-guideline study *No data*	Methacrylamide *Rat/NS/NS*	- Inhalation *4 hours*	Not specified	-	LC0: 0.01 mg/L air
Exp NS Acute toxicity: inhalation.002	3/non-guideline study *No data*	Methacrylamide *Mouse/NS/NS*	- Inhalation *4 hours*	Not specified	-	-
Exp NS Acute toxicity: inhalation.003	3/non-guideline study *No data*	Methacrylamide *Human*	- Inhalation -	Not specified	-	TCLo: 0.003-0.01 mg/L air

Acute toxicity: dermal

A 5-week dermal repeated dose toxicity study in new-born New Zealand White rabbits of both sexes at dose levels 0, 5, 50 and 500 mg/kg/day is reported as a key "weight of evidence" study (Exp WoE Acute toxicity: dermal.001). The study was assigned a reliability score of 2 (reliable with restrictions). No mortality was seen at any of the dose levels. Clinical signs of neurotoxicity were seen in 15/23 animals at 500 mg/kg/day, including splaying and forward extension of the hindlimbs. The incidence and severity of the effects increased during the administration and were reversible within 20 days after the last administration. The estimated LDLo was >500 mg/kg bw.

An acute dermal toxicity study in rats with reliability 2 (reliable with restrictions) is reported as a supporting study (Exp Supporting Acute toxicity: dermal.004). 10% or 20% solution of the Substance was applied for 4 hours to abdominal skin, corresponding to ca 10% of the body surface. No mortality was observed. The only effect seen was temporary apathy, but this effect was present also in the controls. The estimated LDLo was >1600 mg/kg bw.

In addition to the key and supporting studies, 2 other studies are also reported in the registration dossier(s). They are briefly summarised in table 11 below. Further information on the studies can be found on the ECHA dissemination webpages.

Table 11: Summary of the dermal acute toxicity studies reported in the registration dossier(s)

Reference	Reliability/ guideline *Deviations from the guideline if any*	Test material *Species/strain/Sex*	No./sex/dose Route *Duration*	Doses	Results	Effect Level
Exp WoE Acute toxicity: dermal.001	2/non-guideline study *5-week repeated dose toxicity study*	Methacrylamide *Rabbit /New Zealand White/ M& F*	24 (M & F) Dermal *5 weeks*	0, 5, 50, 500 mg/kg/day	No mortality occurred. Clinical signs of neurotoxicity were seen in 15/23 animals at 500 mg/kg/day, including splaying and forward extension of the hindlimbs. The incidence and severity of the effects increased during the administration and were reversible within 20 days after the last administration.	LDLo: >500 mg/kg bw
Exp Supporting Acute toxicity: dermal.004	2/non-guideline study *Rats were dermally exposed to 10% and 20% solutions of methacrylamide for 4 hours to 10% of body surface area. No further information available.*	Methacrylamide *Rat/NS /NS*	10 Dermal: abdominal skin *4 hours*	0, 10%, 20% solutions	No mortality occurred. Only temporary apathy just like in the control group was observed.	LDLo: >1600 mg/kg bw
Exp NS Acute toxicity: dermal.002	3/non-guideline study *No data*	Methacrylamide *Mouse /NS/NS*	- Dermal -	Not specified	-	LD50: >6000 mg/kg bw
Exp NS Acute toxicity: dermal.003	3/non-guideline study *No data*	Methacrylamide *Rat/NS /NS*	- Dermal -	Not specified	-	LD50: >6000 mg/kg bw

Acute toxicity: other routes

Six studies on acute toxicity via other routes are reported in the registration dossier(s). They are briefly summarised in table 12 below. Further information on the studies can be found on the ECHA dissemination webpages.

Table 12: Summary of the acute toxicity studies via other routes reported in the registration dossier(s)

Reference	Reliability /guideline *Deviations from the guideline if any*	Test material *Species/strain/Sex*	No./sex/dose Route	Doses	Results	Effect Level
Exp NS Acute toxicity: other routes.005	2/non-guideline study *Range finding test*	Methacrylamide *Mouse /NMRI/ F*	2 Intraperitoneal	2%, 4% emulsion in oleum arachidis	-	LD100: 1200 mg/kg bw
Exp NS Acute toxicity: other routes.006	2/non-guideline study *No data*	Methacrylamide *Mouse /NS/NS*	- Intraperitoneal	8% in aqueous solution	-	ALD50: ca 450 mg/kg bw
Exp NS Acute toxicity: other routes.003	2/non-guideline study *No data*	Methacrylamide *Rat/NS /NS*	- Intraperitoneal	1%, 10% in aqueous solution	-	ALD50: ca 1300 mg/kg bw
Exp NS Acute toxicity: other routes.004	2/non-guideline study *No data*	Methacrylamide *Mouse /NS/NS*	- Intravenous	1%, 10% in aqueous solution	-	ALD50: 360 mg/kg bw
Exp NS Acute toxicity: other routes.002	2/non-guideline study *No data*	Methacrylamide *Mouse /NS/NS*	- Subcutaneous	1%, 10% in aqueous solution	-	ALD50: ca 500 mg/kg bw
NS Acute toxicity: other routes.001	-/non-guideline study *No data*	Methacrylamide *Mouse /NS/NS*	- Intraperitoneal	Not specified	-	LD50: 200 mg/kg bw

Summary of acute toxicity

The registrant(s) have self-classified the Substance as Acute Tox. 4 H302: Harmful if swallowed. Based on the available information the eMSCA can support this conclusion.

Corrosion/Irritation

Seven studies on skin irritation and 3 studies on eye irritation are reported in the registration dossier(s). A GLP compliant skin irritation study with reliability 1 (reliable without restrictions) performed according to the test method EU B.4., which is equivalent to OECD TG 404 (Acute Dermal Irritation / Corrosion), is reported as a key study for skin irritation (Exp Key Skin irritation / corrosion.006). New Zealand White rabbits were dermally exposed to 0.5 g the Substance (>98%) for 4 hours to 100 cm^2 of body surface area. The primary irritation score was 1.11 out of 8, and the Substance was reported as slightly irritating. Another GLP compliant study according to OECD TG 404, in the same species and with the same exposure concentration, is also reported in the registration dossier(s) (Exp Supporting Skin irritation / corrosion.002). In this study, the Substance was reported as not irritating. In the other studies on skin irritation, the Substance was either reported as slightly irritating or not irritating. For eye irritation, a GLP compliant study performed according to the test method EU B.5., which is equivalent to OECD TG 405 (Acute Eye Irritation / Corrosion), is reported as a key study (Exp Key Eye irritation.002). In this study, a primary irritation score of 3.84 out of 4 was reported, and the Substance was classified as "2B, mildly irritating to eyes" according to GHS.

Summary of corrosion/irritation

The registrant(s) have self-classified the Substance as Eye Irrit. 2 H319: Causes serious eye irritation, and it doesn't warrant classification for skin irritation. Based on the available information the eMSCA can support this conclusion.

7.9.3. Sensitisation

A GLP compliant Local Lymph Node Assay (LLNA) performed according to OECD TG 429 is reported as a key study (Exp Key Skin sensitisation.002). Female mice of CBA/CaOlaHsd strain were tested with concentrations of 5, 10 and 25%. No clinical signs or mortality was observed. The Stimulation Indexes were 0.94, 1.03 and 1.60 for respective test item concentration. An EC3 value could not be calculated since all Stimulation Indexes were below 3.

Two non-guideline skin sensitisation studies in guinea pig are also reported in the registration dossier(s) (Exp NS Skin sensitisation.001, Exp NS Skin sensitisation.003). The Substance is reported as not sensitising to skin in one of the studies, and as slightly sensitising in the other. However, this study was assigned a reliability score of 3 (not reliable).

Summary of sensitisation

The registrant(s) concluded that the Substance is not sensitising. Based on the available information the eMSCA can support this conclusion.

7.9.4. Repeated dose toxicity

Repeated dose toxicity: oral

A 12-month repeated dose toxicity study in male rats of Wistar strain given the Substance in drinking water at dose levels 0, 200, 400, 800 and 1200 ppm (equivalent to ca 0, 4.6, 9.1, 19.5 and 31.6 mg/kg bw/day) is reported as a key study (Exp Key Repeated dose toxicity: oral.013) in the registration dossier(s). The study was assigned a reliability score of 2 (reliable with restrictions). At 800 ppm and higher, significant reduction of rotarod performance, distension in the urinary bladder, shrinkage, and loss of myelinated fibres of the sciatic nerve and atrophy of the gastrocnemius muscle were observed. During the 12-month post-administration period, symptoms of neuropathy were advanced, and pigmentation of fur due to urinary incontinence was observed at 800 and 1200 ppm. In the highest dose group (1200 ppm) symptoms of peripheral neuropathy including hindlimb weakness and abnormal gait were observed, and there was also a significant increase in

serum total cholesterol and phospholipid. Based on neurotoxic effects seen at 800 and 1200 ppm, the NOAEL in this study was ca 9.1 mg/kg bw/day. This NOAEL was subsequently used in the chemical safety assessment to derive long- and short-term systemic DNELs for dermal route.

A 12-month repeated dose toxicity study in male mice of ddY strain given the Substance in drinking water at dose levels 0, 200, 400, 800 and 1200 ppm (equivalent to ca 0, 24.3, 49.6, 120 and 220 mg/kg bw/day) is reported as a supporting study (Exp Supporting Repeated dose toxicity: oral.004). The study was assigned a reliability score of 2 (reliable with restrictions). At 800 ppm and higher, significant reduction of rotarod performance, hindlimb weakness, abnormal gait, distension of the urinary bladder, shrinkage and loss of myelinated fibres and group atrophy of the gastrocnemius muscle were observed. During the 12 month post-administration period, symptoms of neuropathy were advanced, and pigmentation of fur due to urinary incontinence was observed. At 400 ppm and higher, paralysis of hindlimb was observed. A high, but dose-unrelated increase of multiple lung tumours was observed to be greater in treatment groups than in control. The NOAEL in this study was ca 24.3 mg/kg bw/day.

A GLP compliant 28-day repeated dose toxicity study by gavage at dose levels 0, 30, 100 and 300 mg/kg bw/day in male and female rats of crj:CD(SD) strain according to OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) is reported as a supporting study (Exp Supporting Repeated dose toxicity: oral.003, Exp Supporting Repeated dose toxicity: oral.009). This study was assigned a reliability score of 1 (reliable without restrictions). Food and water consumption was decreased in both sexes at 300 mg/kg/day. Body weights and body weight gains were decreased in males at 300 mg/kg/day and females at 100 mg/kg/day. Clinical and functional signs of neurotoxicity including staggering gait, decreased muscle tone and ataxia were seen in both sexes at 300 mg/kg/day. Males at 300 mg/kg/day also showed decreased grip strength. Males at 100 mg/kg/day or more, and females at 30 mg/kg/day or more, showed decrease in locomotor activity. At the end of recovery period, staggering gait, ataxia, decreased muscle tone, decreased locomotor activity and decreased grip strength were seen in animals of both sexes. In addition, males also showed splay of hindlimb. Histopathological examinations revealed slight swelling of axons in the cerebellar peduncle and slight or moderate degeneration of sciatic nerve fibres at 300 mg/kg/day for both sexes. Additional histopathological findings in males were moderate cellular infiltration of neutrophil (2/7 animals) and granuloma (1/7 animals) in the lungs, slight cellular infiltration of neutrophil at lamina propria in the trachea (1/7 animals), slight hyperplasia of tubular pars nervosa in the pituitary gland and retention of step 19 spermatids at stage IX and X in testis (1/7 animals). Additional histopathological findings in females were slight granulation of muscular layer in the oesophagus (1/7 animals), slight dilation of renal pelvis in the kidney (1/7 animals) and slight cyst in the pituitary gland (1/7 animals) and uterus (1/7 animals). Absolute organ weights of brain, lungs, heart, liver, spleen, and pituitary gland were decreased at 300 mg/kg/day for both sexes. (adrenals – males, thymus - females). Relative organ weights of brain, lungs, heart, liver, and kidney were increased at 300 mg/kg/day for both sexes. The relative organ weight of thyroids, testes and epididymides were increased in males at 300 mg/kg/day (female – thymus). In both sexes, at 300 mg/kg/day, a decrease in haematocrit, haemoglobin, MCH, urea nitrogen, creatinine, alpha1-globulin and ALP, and an increase in albumin and triglyceride were noted. In males, at 100 mg/kg/day, a decrease in haemoglobin and MCH were noted. In males, at all dose levels, a decrease in MCV was noted. The NOAELs in this study were considered to be 30 mg/kg bw/day for males and <30 mg/kg bw/day for females.

In addition to the key and supporting studies, 12 other studies are also reported in the registration dossier(s). They are briefly summarised in table 13 below. Further information on the studies can be found on the ECHA dissemination webpages.

Table 13: Summary of the oral repeated dose toxicity studies reported in the registration dossier(s)

Reference	Reliability/ guideline ***Deviations from the guideline, if any / Parameters investigated in the non-guideline study***	Test material ***Species/strain/Sex***	No./sex /dose Route ***Duration***	Doses	Results	Effect Level
Exp Key Repeated dose toxicity: oral.013	2/non-guideline study *Clinical signs, functional findings, mortality, body weight, haematology, clinical biochemistry, urinalysis, organ weights, gross pathology*	Methacrylamide *Rat/Wistar/M*	18 to 20 Oral: drinking water *4, 8 and 12 months*	0, 200, 400, 800, 1200 ppm equivalent to ca: 0, 4.6, 9.1, 19.5, 31.6 mg/kg/day	Effects at 800 and/or 1200 ppm: Symptoms of peripheral neuropathy including hindlimb weakness, abnormal gait and decreased rotarod performance. Shrinkage and loss of myelinated fibres of the sciatic nerve and atrophy of the gastrocnemius muscle. During post-administration period, pigmentation of body fur due to urinary incontinence was seen, and neuropathy was advanced. Statistically significant dose related increases of serum total cholesterol and phospholipid content were seen after 12 months in highest dose group.	NOAEL: 9.1 mg/kg bw/day LOAEL: 19.5 mg/kg bw/day
Exp Supporting Repeated dose toxicity: oral.003	1/OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents)	Methacrylamide *Rat/Crj: CD (SD)/M*	7 Oral: gavage *28 days*	0, 30, 100, 300 mg/kg/day	Effects at high and/or mid doses: Decrease in body weight in high dose group. Clinical observations of neurotoxicity in mid and high dose group, including staggering gait, ataxia, decrease in muscle tone and grip strength and decrease in locomotor activity counts. These effects were still seen at the end of recovery period, in addition to splay of hindlimb. Histopathological changes in the nervous system in the high dose group (number of animals): slight swelling of axonal in the cerebellar peduncle (1), slight degeneration of sciatic nerve fibres (1) and moderate cellular infiltration of neutrophil (7). At the end of recovery period: slight swelling of axonal in the cerebellar peduncle (3), slight (4) or moderate (3) degeneration	NOAEL: 30 mg/kg bw/day

Reference	Reliability/ guideline *Deviations from the guideline, if any / Parameters investigated in the non-guideline study*	Test material *Species/strain/Sex*	No./sex /dose Route *Duration*	Doses	Results	Effect Level
					of sciatic nerve fibres. Histopathological changes of the lungs in high dose group. Decrease in absolute organ weight of the brain, lungs, heart, liver, adrenals, spleen, and pituitary gland in high dose group, and of the heart, liver and epididymides in mid dose group. Increase in relative organ weight of several organs in mid and high dose group, including brain, lungs, kidneys, and testes. Haematological findings at all dose levels. Decrease in MCV in low and mid dose group, but not in high dose group. Slight hyperplasia of tubular pars nervosa in the pituitary gland in one animal in high dose group.	
Exp Supporting Repeated dose toxicity: oral.009	1/OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents)	Methacrylamide *Rat/Crj: CD (SD)/F*	7 Oral: gavage *28 days*	0, 30, 100, 300 mg/kg/day	Clinical observations of neurotoxicity in low and high dose group. The observations in the high dose group were staggering gait, ataxia and decrease in muscle tone; and in low dose group decrease in locomotor activity counts. All effects seen in high dose group were still seen at the end of recovery period, in addition to decreased locomotor activity counts and decreased hindlimb grip strength. Decrease in body weight gain in mid dose group. Haematological findings in high dose group. Decrease in absolute organ weight of the brain, lungs, heart, liver, spleen, pituitary gland and thymus, and increase in relative organ weight of brain, lungs, heart, liver and kidneys in high dose group. Histopathological changes of the nervous system in the high dose group	NOAEL: <30 mg/kg bw/day

Reference	Reliability/ guideline *Deviations from the guideline, if any / Parameters investigated in the non-guideline study*	Test material *Species/strain/Sex*	No./sex /dose Route *Duration*	Doses	Results	Effect Level
					(number of animals): slight swelling of axonal in the cerebellar peduncle (2), slight degeneration of sciatic nerve fibres (7), slight granulation of muscular layer in the oesophagus (1). At the end of recovery period: slight swelling of axonal in the cerebellar peduncle (5), slight (5) or moderate (2) degeneration of sciatic nerve fibres. Slight cysts found in the pituitary gland and uterus in two animals in the high dose group.	
Exp Supporting Repeated dose toxicity: oral.004	2/non-guideline study *Clinical signs, functional findings, mortality, body weight, haematology, clinical biochemistry, urinalysis, organ weights, gross pathology*	Methacrylamide *Mouse/ddY/M*	18 to 20 Oral: drinking water *4, 8 and 12 months*	0, 200, 400, 800, 1200 ppm equivalent to ca: 0, 24.3, 49.6, 120, 220 mg/kg/day	800 and/or 1200 ppm: Body weight gain decreased significantly. Symptoms of peripheral neuropathy including hindlimb weakness, abnormal gait and decreased rotarod performance. Shrinkage and loss of myelinated fibres of sciatic nerve and group atrophy of gastrocnemius muscle. During post-administration period, pigmentation of body fur due to urinary incontinence was seen, and neuropathy was advanced. 400 ppm and higher: Paralysis of hindlimb. "A high but dose-unrelated increase of multiple lung tumours […] was observed to be greater in the treatment groups than in the control".	NOAEL: 24.3 mg/kg bw/day
Exp NS Repeated dose toxicity: oral.014	2/non-guideline study *Body weight, rotarod performance, histopathological study of Sciatic*	Methacrylamide *Rat/Wistar/M*	4 Oral: drinking water *60 to 90 days*	0, 140, 210, 320, 480 mg/kg/day	480 mg/kg/day: Morphological changes in tibial and sural nerve (shrinkage and loss of myelinated fibres, myelin retraction and corrugated myelin sheets). Significant decrease in [3H]Cholchicine-binding to neurotubulin in nerve	NOAEL: 210 mg/kg bw/day

Reference	Reliability/ guideline ***Deviations from the guideline, if any / Parameters investigated in the non-guideline study***	Test material ***Species/strain/Sex***	No./sex /dose Route ***Duration***	Doses	Results	Effect Level
	nerve, [3H]Colchicine-binding to neurotubulin nerve tissues (sciatic nerves, cortex, medulla cerebellum and spinal cord)				tissues. From 320 mg/kg/day: Signs of ataxia, i.e., weakness and a tendency towards spreading and dragging of hindlimb. Urinary incontinence seen in animals showing severe clinical signs. Significant suppressions of body weight at all dose levels.	
Exp NS Repeated dose toxicity: oral.005	2/non-guideline study *Not specified, "14-day oral toxicity"*	Methacrylamide *Mouse/CF1 /M&F*	10 Oral: gavage *14 days*	0, 125, 250, 500 mg/kg/day	High dose: 10 out of 20 animals died. Haemorrhages of the lungs. Mid and high dose: Reduced food intake and body weight gain. Neurotoxic symptoms including disturbance of coordination, splay of hindlimb, decreased righting reflex, ataxia, slight tremor, and slight cyanosis.	NOAEL: 125 mg/kg bw/day LOAEL: 250 mg/kg bw/day
NS Repeated dose toxicity: oral.010	2/non-guideline study *Body weight, observations of stance and gait, hindlimb activity by ability to grasp a sloping bar*	Methacrylamide *Rat/Porton /M*	6 Oral: feed *25 days*	50 mg/kg (11 days) followed by 100 mg/kg (14 days) Cumulative dose: 1500 mg/kg	No neurotoxic effects.	-
Exp NS Repeated dose toxicity: oral.008	3/non-guideline study *Not specified, documentation of method insufficient for assessment*	Methacrylamide *Rat, mouse and rabbit*	- Oral: drinking water -	0.05 – 1 mg/kg/day	"A daily dose of 0.05 – 1.0 mg/kg decreased cholinesterase activity in blood, increased the concentration of ascorbic acid in kidneys, and decreased the conditioned reflexes of the tested animals."	-

Reference	Reliability/ guideline ***Deviations from the guideline, if any / Parameters investigated in the non-guideline study***	Test material ***Species/strain/Sex***	No./sex /dose Route ***Duration***	Doses	Results	Effect Level
Exp NS Repeated dose toxicity: oral.016	3/non-guideline study *Not specified, only summary available*	Methacrylamide *Rabbit/not specified/M&F*	1 to 3 Oral: gavage *Maximal 10 ½ weeks*	100, 250, 500 mg/kg	High dose: Paralysis, loss of appetite, diarrhoea, and trembling. Increase in left-shift leucocytes prior to death. Mid dose: Parese, paralysis, loss of appetite and diarrhoea. 2 of the 3 animals died or had to be killed before the end of the study. Low dose: No signs of toxicity. Both animals died, but deaths appeared not to be treatment related. Urine analysis revealed evidence of slight kidney damage at all dose levels, but there were no confirmatory histopathological findings.	NOAEL: <100 mg/kg bw/day
Exp NS Repeated dose toxicity: oral.015	3/non-guideline study *Not specified, only summary available*	Methacrylamide *Cat/not specified/M&F*	Low: 5 Mid: 8 High: 2 (M&F) Oral: gavage *9 weeks*	4-45 x 100 mg/kg, 3-6 x 250 mg/kg, 2 x 500 mg/kg	Neurotoxic effects observed: Disturbance of gait, restlessness, spasm-like convulsions, excitation, balance disturbance, spastic pareses and paralysis. Loss of appetite. Recovery of surviving animals within 7 months. Mortality: 500 mg/kg: 1/2 animals 250 mg/kg: 2/8 animals 100 mg/kg: 2/5 animals	NOAEL: <100 mg/kg bw/day
Exp NS Repeated dose toxicity: oral.012	3/non-guideline study *Not specified, only summary available*	Methacrylamide *Dog/not specified/M&F*	4 in total Oral: gavage *7 months to ca 2 ½ years*	0, 100 following 200, 300, 8 or 9 x 200 following 4 x 300 mg/kg/day	After daily dosing of 100 mg/kg: No typical neurotoxic effects (tremor spastic parese and ataxia). After daily dosing of 200 mg/kg: Loss of appetite, trembling, spastic paresis of the hindlimbs and disturbed gait. After weekly dosing of 300 mg/kg: Spastic walk, which persisted. After the 4th dose, one dog developed	NOAEL: 100 mg/kg bw/day

Reference	Reliability/ guideline *Deviations from the guideline, if any / Parameters investigated in the non-guideline study*	Test material *Species/strain/Sex*	No./sex /dose Route *Duration*	Doses	Results	Effect Level
					tremor, spastic paresis of the hindlimbs and tonic-clonic cramps. After 7 days, the animal recovered to a small extent. The symptoms were not reversible within 8 years.	
Exp NS Repeated dose toxicity: oral.007	3/non-guideline study *Not specified, only summary available*	Methacrylamide *Dog/NS/NS*	9 Oral: gavage -	200-500 mg/kg	6 dogs died after 2-6 doses. Neuropathological findings in the one dog examined after 23 days of dosing largely normal, except for reduced orientation and spontaneous activity when eyes were covered. Clinical observations: Decreased body weight. Slightly increased blood-urea levels and slight pathological kidney damage. Slightly increased number of glial cells in the one dog examined.	-
Exp NS Repeated dose toxicity: oral.001	3/non-guideline study *Not specified, only summary available*	Methacrylamide *Dog/NS/NS*	1 Oral: feed *15 or 28 days*	1 x 500 mg/kg followed by 14 x 200 mg/kg or 27 x 200 mg/kg	Clinical signs of neurotoxicity after daily dosing of 200 mg/kg: Stiffness of hindlimbs, over excitation, severe and prolonged tremors (particularly in the rear half) for one of the dogs. One dog still had slight ataxia 14 months post-treatment. The other dog developed spastic paresis after 28 doses, and eventually died in convulsion. "No specific changes were indicated on autopsy."	-
Exp NS Repeated dose toxicity: oral.002	4/non-guideline study *Not specified, only summary available*	Methacrylamide *Rat/Not specified/M&F*	10 Oral *35 or 95 days*	35 days: 0, 360-380 mg/kg/day 95 days: 0, 43-44 mg/kg/day	360-380 mg/kg/day: Increased mortality compared to control. Reduced body weight. Neurotoxic effects: excitation, paralysis of hindlimb.	NOAEL: 43 mg/kg

Reference	Reliability/ guideline ***Deviations from the guideline, if any / Parameters investigated in the non-guideline study***	Test material ***Species/strain/Sex***	No./sex /dose Route ***Duration***	Doses	Results	Effect Level
Exp NS Repeated dose toxicity: oral.011	4/non-guideline study NTP study *Rotarod performance, histopathological examination and weighting of testis, examination of blood (red and white blood cell counts, haemoglobin concentration, haematocrit value and differentiation of white blood cells), effect of metabolic activation by intraperitoneal injection of Phenobarbital in test animals.*	Methacrylamide *Mouse/ddY/M*	5 Oral: gavage *8-10 weeks twice a week*	0, 153 mg/kg	Neurotoxic effects: ataxia of the hindlimbs, slight behavioural changes (aggressiveness, alertness), reduction of rotarod performance about 50%. Phenobarbital treatment reduced the neurotoxic effects.	-
Exp NS Repeated dose toxicity: oral.006	4/ non-guideline study *"Subacute screening toxicity study". Gross pathology. No further information available.*	Methacrylamide *Rat/not specified/M*	6 Oral: gavage *14 days*	450 mg/kg bw	Reduced body weight during the first week. At day 10 of dosing "3 rats showed tremors, circling, chewing on tail, lack of balance, and spasms appearing to originate in the hind quarters. The other 3 rats were nervous and irritable but did not show the other symptoms". 1 rat showed mottled lung and 1 rat atelectasis in the lungs.	-

Repeated dose toxicity: inhalation

A GLP compliant 90-day inhalation repeated dose toxicity study with reliability 1 (reliable without restrictions) according to OECD TG 413 (Subchronic Inhalation Toxicity: 90-Day, before 2009) is reported as a key study (Exp Key Repeated dose toxicity: inhalation.002). Wistar rats of both sexes were exposed (nose only) to concentrations of 0, 10, 25 and 62.5 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks. No neurotoxicity was observed. Male body weights and body weight gains were significantly decreased at 25 and 62.5 mg/m^3, and the group mean terminal body weight was 11.0% and 12.7% lower than control, respectively, at the end of the 13-week exposure. Change in food intake was minor. Female body weights, with one exception on Day 22, did not significantly differentiate from control at any of the dose levels. Absolute organ weight of the lungs was reduced by 7.7% and 8.5% in males at 25 and 62.5 mg/m^3, respectively. Absolute brain weight was reduced by 4.3% and absolute kidney weight was reduced by 8.5% in males at 25 mg/m^3. Relative organ weights of the heart and testes were increased in males at 25 and 62.5 mg/m^3. Female organ weights were not affected. Several haematological and clinical biochemistry parameters were significantly changed compared to control but was not considered as relevant because they lacked dose-response relationship, were restricted to one sex and/or were in the range of historical control data. Histopathological examination revealed findings of degeneration, squamous metaplasia and/or respiratory metaplasia of olfactory mucosa in nasal cavity level IV at 25 and 62.5 mg/m^3. These findings were of an adverse character, and **the local NOAEC was 10 mg/m^3**. The registrant(s) did not consider the reduction of absolute brain and kidney weights as adverse since "*they were minor in degree, were not dose-related and there were no confirmatory histopathology findings in the brain or kidneys in high dose animals*". The other changes in organ weights were considered by the registrant(s) "*to be a reflection of the effects on body weights in these groups, rather than representing a primary effect of the test item on these organs*". The significantly reduced body weights in males at 25 and 62.5 mg/m^3 "*were considered to be only moderate in degree, as they were restricted to one gender, relevant body weight loss was not evident during the study, and by the end of the 13-week treatment period the group mean body weights of mid- and high-dose males were only 9.3% lower than the concurrent control animals*". Thus, the registrant(s) set the systemic NOAEC at 62.5 mg/m^3, the highest dose administered. The systemic and local NOAECs from this study were subsequently used in the chemical safety assessment to derive the DNELs for local and systemic effects via inhalation route. The eMSCA does not agree with the setting of the systemic NOAEC. **According to the eMSCA the systemic NOAEC should be 10 mg/m^3, because of the decreased body weight and decreased organ weights observed at next dose levels.**

A GLP compliant 14-day range finding study for a 28-day subacute inhalation study with reliability 2 (reliable with restrictions) is reported as a supporting study (Exp Supporting Repeated dose toxicity: inhalation.003). Male rats of Sprague-Dawley strain were exposed to concentrations of 0.030, 12.8, 62.6 and 286 mg/m^3 for 6 hours/day, 7 days/week for 2 weeks. No mortality or neurotoxicity was observed. Histopathological examination revealed central lobular hepatocellular hypertrophy in the liver and squamous/squamoid metaplasia of the columnar epithelium covering the central seromucous gland in the larynx at 62.6 and 286 mg/m^3. However, these organs were not examined at 12.8 mg/m^3. Based on these changes, the NOAEC was 12.8 mg/m^3.

In addition to the key and supporting studies, one more study is also reported in the registration dossier(s). It is briefly summarised in table 14 below. Further information on the study can be found on the ECHA dissemination webpages.

Table 14: Summary of the inhalation repeated dose toxicity studies reported in the registration dossier(s)

Reference	Reliability/ guideline ***Deviations from the guideline, if any / Parameters investigated in the non-guideline study***	Test material ***Species/strain/Sex***	No./sex /dose Route ***Duration***	Doses	Results	Effect Level
Exp Key Repeated dose toxicity: inhalation.002	1/OECD TG 413 (Subchronic Inhalation Toxicity: 90-Day Study)	Methacrylamide *Rat/Wistar/ M&F*	10 Inhalation: nose only *13 weeks*	0, 10, 25, 62.5 mg/m³	Reduction of male body weight and body weight gain at mid and high dose levels. Decrease in absolute lung weight in mid and high dose males, increase in relative organ weight for heart and testes in mid and high dose males. Absolute brain and kidney weights reduced in mid dose males. Degeneration, squamous metaplasia, and respiratory metaplasia of olfactory mucosa in nasal cavity level IV at mid and high dose levels.	Local NOAEL: 10 mg/m³ Systemic NOAEL: 62.5 mg/m³ Remark: according to the eMSCA the systemic NOAEL should be 10 mg/m³ because of the decreased body weight and changes in organ weights observed at next dose levels.
Exp Supporting Repeated dose toxicity: inhalation.003	2/non-guideline study *Cage side observations, detailed clinical observations, food and water consumption, grip strength, post-mortem necropsy, complete macroscopic post-mortem examinations of the external surface and all orifices, organ weights (brains and testes, with epididymides); and histopathological*	Methacrylamide *Rat/Sprague-Dawley/M*	5 Inhalation: nose only *14 days*	0.030, 12.8, 62.6, 286 mg/m³ (Analytical conc.)	Histopathological effects in the liver and larynx at mid and high dose levels (central lobular hepatocellular hypertrophy in the liver and squamous/squamoid metaplasia of the columnar epithelium covering the central seromucous gland in the larynx).	NOAEL: 12.8 mg/m³

Reference	Reliability/ guideline *Deviations from the guideline, if any / Parameters investigated in the non-guideline study*	Test material *Species/strain/Sex*	No./sex /dose Route *Duration*	Doses	Results	Effect Level
	examination of several tissues. Slides of these tissues were also examined microscopically for all animals in control, mid and high-exposure groups.					
Exp NS Repeated dose toxicity: inhalation.001	4/non-guideline study *Not specified, Russian study: only partial translation into English available*	Methacrylamide *Rat/NS/NS*	6 Inhalation *16 weeks*	0, 3.2, 12.0, 34.5 mg/m^3	Behavioural changes and biochemical changes in the brain at mid and high dose levels (increase in hydroxyindol acetic acid and histidine levels). Dystrophic changes in the liver, kidney and brain at high dose level. Slightly smaller testes, and tendency for reduced mobility of spermatozoa at high dose level.	NOAEL: 3.2 mg/m^3

Repeated dose toxicity: dermal

A subacute repeated dose toxicity study via dermal route in male and female rabbits at dose levels 0, 5, 50 and 500 mg/kg/day is reported as a supporting study (Exp Supporting Repeated dose toxicity: dermal.005). The study was assigned a reliability score of 2 (reliable with restrictions). Rabbits were dosed for 12 weeks, except for the 500 mg/kg/day group for which week 6-12 served as a recovery period. No mortality was observed. Clinical signs of neurotoxicity were seen in 15/23 animals at 500 mg/kg/day, including splaying and forward extension of the hindlimbs. The incidence and severity of the effects increased during the administration, and were reversible within 20 days after the last administration. The NOAEL in this study was considered to be 50 mg/kg/day.

In addition to the supporting study, 4 other studies are also reported in the registration dossier(s). They are briefly summarised in table 15 below. Further information on the studies can be found on the ECHA dissemination webpages.

Table 15: Summary of the dermal repeated dose toxicity studies reported in the registration dossier(s)

Reference	Reliability/guideline ***Deviations from the guideline, if any / Parameters investigated in the non-guideline study***	Test material ***Species /strain/ Sex***	No./sex /dose Route ***Duration***	Doses	Results	Effect Level
Exp Supporting Repeated dose toxicity: dermal.005	2/non-guideline study *Detailed clinical observations, haematology, clinical chemistry, neurobehavioral examination, gross pathology and organ weights (no details reported), histopathology (non-neoplastic, no details reported)*	Methacrylamide *Newborn rabbit/New Zealand White/M&F*	24 (M&F) Dermal *5 or 12 weeks*	0, 5, 50 mg/kg/day (12 weeks) 0, 5, 50, 500 mg/kg/day (5 weeks)	Clinical signs of neurotoxicity at highest dose level, including splaying and forward extension of the hindlimbs. The effects increased in incidence and severity during the administration and were reversible within 20 days after the last administration.	NOAEL: 50 mg/kg LDLo: >500 mg/kg
Exp NS Repeated dose toxicity: dermal.003	4/non-guideline study *Blood and urine analysis, autopsy. No further information available.*	Methacrylamide *Rabbit/not specified/M*	- Dermal -	0, 21 x (20% in vehicle; ca 700 or 800 mg/kg)	Toxicity not observed.	NOAEL: ca 700 mg/kg
Exp NS Repeated dose toxicity: dermal.002	4/non-guideline study *Not specified, only summary available*	Methacrylamide *Rat/NS/NS*	- Dermal *12 days*	0, 200, 400 mg/rat	"Apathy and temporary reeling."	-
Exp NS Repeated dose toxicity: dermal.001	4/non-guideline study *Not specified, only summary available*	Methacrylamide *Guinea pig/NS/NS*	10 Dermal *4 weeks*	0, 1000 mg/kg (20% in vehicle as a paste)	"4 animals died after 6 or 10 applications. Prior to death, a slight tremor was observed. Local effect: Slight skin irritation."	-
Exp NS Repeated dose toxicity: dermal.004	4/non-guideline study *Not specified, only summary available*	Methacrylamide *Rabbit/not specified/M&F*	3 in total Dermal *Frequency of treatment: 1 x 24 h following 20 x 8 h*	0, 1 g/animal	Toxicity not observed. No skin effects.	-

Repeated dose toxicity: other routes

Table 16: Summary of the intraperitoneal repeated dose toxicity via study reported in the registration dossier(s)

Reference	Reliability/guideline *Deviations from the guideline, if any / Parameters investigated in the non-guideline study*	Test material *Species/strain/Sex*	No./sex/dose Route *Duration*	Doses	Results	Effect Level
Repeated dose toxicity: other routes	2/non-guideline study *No data available on method*	Methacrylamide *Cat/NS/NS*	3 in total Intraperitoneal *3 weeks*	Steadily increasing from 30-120 mg/kg/day (total dose: 900 mg/kg)	Neurotoxicity not observed.	-

Summary of repeated dose toxicity

Clinical signs of neurotoxicity, as well as histopathological changes in the nervous system, were observed in several of the oral repeated dose toxicity studies. The LOAEL for neurotoxicity was 19.5 mg/kg/day, from the 12-month oral repeated dose toxicity study in male rats (Exp Key Repeated dose toxicity: oral.013). The NOAEL of 9.1 mg/kg bw/day from this study was used for the derivation of the systemic dermal and oral DNELs. Signs of neurotoxicity and systemic toxicity at lower dose levels (0.05-0.01 mg/kg/day) were reported in a study in rabbits, rats, and mice (Exp NS Repeated dose toxicity: oral.008). However, the documentation of this study was insufficient for assessment, and the study was assigned a reliability score of 3 (not reliable). The Substance also caused systemic toxicity in several of the studies, including haematological effects, decreased body weights, decreased organ weights and histopathological changes of the organs. Generally, signs of systemic toxicity were seen at higher dose levels than those at which neurotoxicity was seen.

Clinical signs of neurotoxicity were also seen in the dermal repeated dose toxicity studies. In the supporting study in rabbits' neurotoxicity was seen at 500 mg/kg bw/day (Exp Supporting Repeated dose toxicity: dermal.005).

No signs of neurotoxicity were reported in the key and supporting inhalation repeated dose toxicity studies. In the other inhalation study reported in the dossier(s), behavioural changes as well as biochemical and dystrophic changes in the brain were seen at 12.0 mg/m^3 and higher (Exp NS Repeated dose toxicity: inhalation.001). However, the reliability of this study is low (reliability 4, not assignable). There are signs of systemic toxicity in both the key and supporting inhalation studies, including histopathological changes, decreased body weight, decreased absolute organ weights and increased relative organ weights. The NOAECs (local: 10 mg/m^3, systemic: 62.5 mg/m^3) from the key study were subsequently used in the derivation of the local and systemic inhalation DNELs. The eMSCA does not agree with the setting of the systemic NOAEC. The eMSCA has used a NOAEC of 10 mg/m^3 from the key study and revised the systemic inhalation DNEL.

The registrant(s) have self-classified the Substance as STOT SE 2 (H371) and STOT RE 2 (H373) for effects on the nervous system, and as STOT SE 3 (H335) for effects on the respiratory tract. Based on the available information the eMSCA can support this conclusion.

7.9.5. Mutagenicity

Two *in vivo* and five *in vitro* studies on mutagenicity are reported in the registration dossier(s).

A bacterial reverse mutation assay with reliability 2 (reliable with restrictions) is reported as a supporting study (Exp Supporting Genetic toxicity in vitro.005; Hashimoto et al., 1985). All results were negative in *Salmonella typhimurium* TA 1535, TA 1537, TA 98, TA 100, and TA 1538 with and without exogenous metabolic activation up to 5000 µg/plate. This study was conducted on several acrylamide analogues. One of the analogues tested, an epoxy derivative of the Substance (glycidyl methacrylamide), was reported as mutagenic. There is currently no information available about the possibility of metabolic conversion of the Substance to glycidyl methacrylamide.

A GLP compliant gene mutation study performed according to "Japan: Guidelines for Screening Mutagenicity Testing of Chemicals" and OECD TG 471 (Bacterial Reverse Mutation Assay) is reported as a key study (Exp Key Genetic toxicity in vitro.004). The study was assigned a reliability score of 1 (reliable without restrictions). All results were negative in *Salmonella typhimurium* TA100, TA1535, TA98 and TA1537 and *Escherichia coli* WP2 uvrA with and without exogenous metabolic activation up to limit concentration 5000 µg/plate. Positive and vehicle controls were reported as valid, although there is no further information on vehicle controls.

A GLP compliant in vitro mammalian chromosome aberration test with reliability 1 (reliable without restrictions) performed according to OECD TG 473 is reported as a key study (Exp Key Genetic toxicity in vitro.001). CHL/IU cell cultures were exposed to the Substance at concentrations of 0, 0.23, 0.45, 0.90 (10.0 mM, limit concentration) mg/ml in the presence and/or absence of metabolic activation. No mutagenicity or cytotoxicity was observed up to limit concentration, 10.0 mM.

Another GLP compliant in vitro mammalian chromosome aberration test performed according to OECD TG 473 is reported in the registration dossier(s) (Exp NS Genetic toxicity in vitro.003). The study was assigned a reliability score of 2 (reliable with restrictions) because several of the concentrations exceeded the limit concentration (10 mM). CHL/IU cell cultures were exposed to the Substance at concentrations of 0, 0.250, 0.625, 1.25, 2.50 and 5.00 (58.7 mM) mg/ml in the presence and/or absence of metabolic activation. The frequency of structural aberrations was significantly higher at 5.00 mg/ml in the absence of metabolic activation. No positive responses were seen below 2.50 mg/ml in the absence of metabolic activations, nor at any of the concentrations in the metabolic activation test. Cytotoxicity was not observed up to the highest concentration (5.00 mg/ml). Since the positive responses were only seen at concentrations above the limit concentration (10 mM) they were not regarded as reflecting a specific mutagenicity of the Substance.

A GLP compliant in vitro mammalian cell gene mutation test with reliability 1 (reliable without restrictions) performed according to OECD TG 476 is reported as a key study (Exp Key Genetic toxicity in vitro.002). HPRT locus in V79 cells of the Chinese hamster was exposed to concentrations of 53.8, 107.5, 215.0, 430.0 and 860.0 (ca 10 mM, limit concentration) µg/mL in the presence and absence of metabolic activation in two independent experiments, using two parallel cultures each. The highest solvent control value slightly exceeded the range of historical control data in one of the parallel cultures, although the mean value of both parallel cultures was within the historical control data. For some concentrations, the number of mutant colonies/10^6 cells were outside the range of historical control data in one of the two parallel cultures. However, the mean was inside the range of historical control data for all concentrations. The number of mutant colonies were not dose dependent. In conclusion, the Substance is not considered to be mutagenic in this assay.

A GLP compliant mammalian erythrocyte micronucleus test with reliability 1 (reliable without restrictions) performed according to OECD TG 474 is reported as a key study (Exp

Key Genetic toxicity in vivo.001). NMRI mice of both sexes were given orally a single dose of the Substance at dose levels 0, 87.5, 175 and 350 mg/kg bw. Samples of the bone marrow were taken after 24 hours at all dose levels, and after 48 hours at 350 mg/kg. There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow at any of the dose levels. All results were in the range of historical control data. Both positive and negative controls were valid.

A GLP compliant dominant lethal assay conducted as a part of a reproductive toxicity study by RACB protocol is reported as a supporting study (Exp Key Genetic toxicity in vivo.002). The study was assigned a reliability score of 2 (reliable with restrictions). Male mice of CD-1 strain were administered the Substance in drinking water at dose levels 24, 80 and 240 ppm (equivalent to ca 4.62-5.08, 15.67-18.54 and 44.17-73.18 mg/kg). "No dominant lethal effect (increase in the number of early resorptions/females, the number of dead foetuses, or in total post implantation loss) was observed".

Summary of mutagenicity

All results were negative in the *in vitro* studies in bacteria and mammalian cells. Furthermore, the result was negative in the mammalian erythrocyte micronucleus test according to OECD TG 474 (Exp Key Genetic toxicity in vivo.001), and no effects were seen in the dominant lethal assay conducted as a part of a reproductive toxicity study by RACB protocol (Exp Key Genetic toxicity in vivo.002). The registrant(s) have not self-classified the Substance for mutagenicity. Based on the available information the eMSCA can support this conclusion.

7.9.6. Carcinogenicity

Two carcinogenicity studies are reported in the registration dossier(s). In one of the studies, mice were administered 200 mg/kg intraperitoneally either daily or 5 times every second day for 5 days, with a post-exposure period of 6 months (Exp NS Carcinogenicity.002). The mice dosed with the Substance had an increased number of lung adenoma compared to control (in 21-28% compared to 2.1%). However, dose-dependency could not be determined as the Substance was only administered at one dose level, and the study lacked documentation on animal husbandry including barrier systems. Therefore, the study was assigned a reliability score of 4 (not assignable). The other study was a GLP compliant initiation promotion study by Bull et al. (1984). Mice were administered the Substance by gavage at dose levels 0, 25, 50 and 100 mg/kg with TPA (12-o-tetra-decanoylphorbol-13-acetate), and 100 mg/kg without TPA for 2 weeks, following 28 weeks post treatment observation (Exp NS Carcinogenicity.001). No increase of neoplasms was noted in this study. Even though this study was well documented and GLP compliant, its validity and reliability has been questioned since acrylamide, a known carcinogen, did not show any tumour initiating potential in this study. Thus, the study was assigned a reliability score of 4 (not assignable).

Summary of carcinogenicity

The Substance is reported as carcinogenic in one of the studies reported in the registration dossier(s), and as not carcinogenic in the other. However, both studies were assigned a reliability score of 4 (not assignable). The registrant(s) have not self-classified the Substance for carcinogenicity. Based on the information available, the eMSCA considers that it is not possible to conclude on the carcinogenicity potential of the Substance.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

A GLP compliant reproduction / developmental toxicity screening test according to OECD TG 421 is reported as a key study for reproductive toxicity (Exp Key Toxicity to reproduction.001). The Substance was administered by gavage to groups of 13 male and 13 female rats of Sprague-Dawley strain at dose levels 0, 12.5, 50 and 200 mg/kg/day. Males were dosed for 42 days and females were dosed for 14 days before mating,

throughout pregnancy to day 3 of lactation. Deaths occurred in one male and 4 females at 200 mg/kg/day, and one female was sacrificed on becoming moribund. Dragging of hindlimb was observed in all animals at 200 mg/kg/day. Body weight gain was decreased in both sexes at 50 and 200 mg/kg/day, and food consumption was decreased in females at 200 mg/kg/day and in males at 50 and 200 mg/kg/day. Histopathological examination revealed inflammation of the lungs, but the reproductive organs were not affected in either sex. Fertility and oestrous cyclicity were not affected. Decreased copulation rate, delayed parturition and abnormal nursing were observed at 200 mg/kg/day. No morphological abnormalities were found in any pups, but low body weight and decreased viability were seen at 200 mg/kg/day. The NOAEL for systemic toxicity was 12.5 mg/kg/day and the NOAEL for reproductive and developmental toxicity was 50 mg/kg/day. Since the reproductive and developmental toxicity were seen only at maternally toxic levels, the effects could be secondary to maternal systemic toxicity.

The registrant(s) have reported the RACB study as the other key study under the 'Toxicity to reproduction' section and as one of the two key studies under the 'Developmental toxicity / teratogenicity' section. In the RACB study (NTP, 1992 and Chapin et al., 1995), the Substance was evaluated for reproductive toxicity, neurotoxicity and dominant lethal effects in Swiss CD-1 mice dosed via drinking water. Following seven days of premating exposure while singly housed, the F0 animals were given the Substance as breeding pairs for 98 days at 24, 80 and 240 ppm (corresponding to 4.5, 15.4 and 49 mg/kg bw/day). The F1 animals were given the same concentrations as the F0 animals (24, 80 and 240 ppm corresponding to 6.8, 23.8 and 71.3 mg/kg bw/day) since weaning (PND 21) until necropsy (week 16) and were mated at 74 (±10) days. The dose levels for F0 animals were set so that the highest dose was expected to cause decreased nerve function halfway through the treatment period and was lower than the maximum tolerated dose. The parameters assessed in F0 and F1 animals were similar including clinical signs, body weights, fertility (ability to produce any live pups), number of litters/pair, number of live pups/litter, sex ratio of the pups, the mean pup weights taken at birth (both absolute and adjusted for pup number), study day of delivery, food and water consumption, and at necropsy the data collected included body and selected organ weights, epididymal sperm number, motility, morphology, and testicular spermatid head count (expressed both as heads/gram of testis and as heads/testis). To assess the dominant lethal effects, the F0 males treated with the Substance for 100 days were cohabited with untreated females for maximum four nights. As an indicator for neurotoxicity, grip strength was evaluated in F0 animals at weeks 0, 6, 9, 12, 15 and 26, and in F1 animals at weeks 3, 5, 7, 10 and 16.

In F0 animals, there were no treatment-related effects on body weights and no consistent changes in food and water consumption. There were no treatment-related neural, reproductive, or somatic organ histopathological effects in F0 animals except statistically significant decrease in epididymal sperm concentrations and spermatid heads/gram of testes in only the mid-dose group, and statistically significant decreased epididymal sperm motility in the high-dose group. There were no dominant lethal effects (increase in the number of early resorptions/females, the number of dead foetuses, or in total post implantation loss).

In F0 males, on weeks 12, 15 and 26, hindlimb grip strength was statistically significantly increased inconsistently at one or more doses. There was also a dose-response related increase in hindlimb grip strength in F0 males in week 6 but these changes did not reach statistical significance. There were no effects on grip strength of forelimb in F0 males and neither of forelimb nor hindlimb in F0 females.

In F1 animals there were no treatment-related effects on neural, reproductive, or somatic organ histopathology, and on fertility, reproductive performance, or terminal body weights. However, the body weights of F1 males were statistically significantly reduced (7% lower compared to controls) in week 3 (at PND 21) for high-dose males (8 and 5% lower but not statistically significantly different compared to controls in low- and mid-dose groups F1 males, respectively). The body weights of F1 females at PND 21 were statistically significantly reduced in low-, mid-, and high-dose groups (7, 6, and 7% lower compared to controls, respectively). At PND 74 (±10), there were no statistically significant changes

in F1 female body weights but that of F1 males were reduced in low-, mid-, and high-dose groups (5, 5, and 6% lower compared to controls, respectively).

During week 3 in F1 males, there was a statistically significant reduction in forelimb grip strength in mid- and high-dose groups (26 and 29% lower compared to controls, respectively; 15% lower in low-dose group – not significant) and in hindlimb grip strength at all dose levels (19, 12, and 31% lower compared to controls in the low-, mid-and high-dose groups, respectively). During week 3 in F1 females the forelimb grip strength was not affected but the hindlimb grip strength was statistically significantly reduced at all dose levels (28, 19, and 32% lower compared to controls in the low-, mid-, and high-dose groups, respectively). However, as the F1 animals grew older the grip strength effects became insignificant and were gone by week 5 except during week 16 when the hindlimb grip strength in the high-dose F1 females was ca. 13% lower compared to controls (not statistically significant) and the hindlimb grip strength of F1 males during week 16 showed dose-response reduction but did not reach statistical significance (ca. 2, 7, and 8% lower compared to controls).

Because of the statistically significant reduction in the hindlimb grip strength during week 3 even in the low-dose F1 animals, it was concluded in the OECD SIDS (2002) evaluation for the Substance that the NOAEL for developmental toxicity is less than 6.8 mg/kg bw/day in the RACB study. The registrant(s), however, report in the registration dossier(s) that the highest dose level (71.3 mg/kg bw/day) is the NOAEL for developmental toxicity in this study because "*the observation of a temporarily slightly diminished grip strength in juvenile mice*" "*is considered as irrelevant for the NOAEL determination*" and they reason that the slightly diminished grip strength cannot be confirmed due to the bias caused by diminished body weights of the treated versus the control animals. The registrant(s) refer to Maurissen et al. (2003) publication which studied the correlation between feed restriction-induced loss of body weight of the rats and the grip strength. Following 13 days of diet restriction, the rats weighed ca. 10% less compared to controls but neither forelimb nor hindlimb grip strengths were affected. Following 24 days of diet restriction, the rats weighed 26% less compared to controls and the forelimb and hindlimb grip strengths were reduced by 18 and 17%, respectively. It is important to note that 11-week-old rats were used in the beginning of the Maurissen et al. study. In the RACB study, all dose groups F1 animals body weights in week 3 (at PND 21) were <10% lower compared to controls yet the hindlimb grip strength reduction ranged between 12 and 31% lower compared to controls in F1 males and between 19 and 32% lower compared to controls in F1 females. Therefore, the reductions in the grip strength of the young F1 mice in the RACB study are not correlated to the degree of their body weight loss.

A GLP compliant prenatal developmental toxicity study performed according to a protocol that is comparable with OECD TG 414 is reported as key study. The Substance was administered by gavage to female mice of Swiss CD-1 strain from gestation days (GD) 6 to 17 at dose levels 0, 30, 60, 120 and 180 mg/kg bw/day. All animals were killed on GD 17 and examined for maternal body weight, implant status, foetal weight, sex, and morphological development. Maternal body weight on GD 17, maternal weight gain during treatment and gestation, and corrected maternal weight gain was decreased at 180 mg/kg bw/day. Relative maternal liver weight was increased at 120 mg/kg/day and higher. Mean foetal body weight per litter was decreased at 120 mg/kg bw/day and higher, and the proportion of dead implants per litter was increased at 180 mg/kg bw/ bwday. The morphological development of the foetus was not affected by the treatment. Both the maternal and the developmental NOAELs were 60 mg/kg bw/day.

Further, a summary from an unpublished study on the Substance given intraperitoneally to mice during gestation days 11-15 at only two dose levels is also reported under the 'Developmental toxicity / teratogenicity' section of the registration dossier(s).

During the SEv the eMSCA concluded that further information was needed to address the concern for developmental neurotoxicity of methylacrylamide. To this end a developmental neurotoxicity study, according to the OECD TG 426, was requested. In this study Wistar Han rats were treated by oral gavage, from day 6 post-coitum to lactation day 20. Doses

were 0, 15, 50 and 150 mg/kg bw/day, based on an initial dose range-finding study. Potential toxicity of the Substance to the structural and functional development of the nervous system was examined in the offspring up to adulthood.

In the F0 (parental) animals, body weight and body weight gain were not affected up to 50 mg/kg bw/day. At 150 mg/kg bw/day mean body weights were about 10% lower throughout the treatment period. Body weight gain was lower during the post-coitum period but was not affected during the lactation period. Adverse clinical signs were piloerection, hunched posture, uncoordinated movements, and abnormal limb gait at 150 mg/kg bw/day. Abnormal gait and uncoordinated movements appeared from lactation day 14 onwards. No changes were noted in maternal care, litter size, live birth index, viability index or weaning index.

In the F1-generation, pre-weaning, no clinical signs, or changes in body weight were recorded up to 50 mg/kg bw/day. At 150 mg/kg bw/day the mean pup body weights were 23% lower for males and females combined, on PND 21 (Table 16). Post-weaning, at 150 mg/kg bw/day reduced mean body weights were reported in both sexes. Body weights were reduced by 10% and 7% in males and females, respectively. This reduction was less pronounced than the decrease in mean pup body weight at this dose throughout the pre-weaning period.

Functional examinations showed no neurotoxicity in the F1 animals at 15 mg/kg bw/day. At 50 mg/kg bw/day reduced startle response and at 150 mg/kg bw/d reduced grip strength, reduced motor activity and reduced startle response was reported.

The grip strength examinations were performed on PND 20, 35 and 60. At 150 mg/kg bw/day grip strength was lower in both sexes (Table 17). The forelimb grip strength was reduced on PND 20 and PND 35 in males and females. The hindlimb grip strength was also reduced in males on PND 20 and 35. On PND 60, the mean hindlimb grip strength of males was reduced, while no effect on forelimb grip strength was reported. Thus, the effect on grip strength was partly recovered towards the completion of the study.

The grip strength was not determined for the F0-animals in this study. In the range-finding study, reduced grip strength was observed at 150 mg/kg bw/day in the F0-females on LD 20 (48% and 60% for fore- and hindlimb, respectively). Reduced grip strength in the F1-animals (28% and 13% for fore- and hindlimb, respectively) was also reported at this dose.

Table 17: Grip strength differences from the controls at 150 mg/kg bw/day in the F1 animals (%)

	PND 20		PND 35		PND 60	
	Forelimb	Hindlimb	Forelimb	Hindlimb	Forelimb	Hindlimb
Males	-45**	-24	-18*	-10	-	-10
Females	-27**	-12	-12	-	-	-14*

Dunnett-test: *5%, **1%

Motor activity was examined on PND 13, 17, 25 and 60. On PND 13 lower mean motor activity for both total movements and ambulation's was reported for females at 150 mg/kg bw/day. Motor activity was reduced by 36% and 53% compared to controls for total movements and ambulation's, respectively. Motor activity was not affected on PND 17, 25 and 60. All groups showed a similar motor activity habituation profile with a decreasing trend in activity over the duration of the test period.

The acoustic startle response was examined by measurement of the average and maximum response amplitudes and latency to maximum response amplitude on PND 25 and 60 (Table 18). On PND 25 a lower average response amplitude was reported at 50 mg/kg bw/day in females. The overall mean for the response amplitude was about 10% lower

compared to controls. At 150 mg/kg bw/day lower average and maximum response amplitudes were reported. The mean average response amplitude was 38% and 30% lower for males and females, respectively. The mean maximum response amplitude was also lower. On PND 60, at 150 mg/kg bw/day the average and maximum response amplitude remained lower for males. The mean average and maximum response amplitude were reduced by 23% and 22%, respectively. In females the mean for the maximum response amplitude was reduced by 15%.

The reduced startle response could not be coupled to reduced grip strength, since reduced startle responses were still evident, while grip strength had partly recovered on PND 60. No histopathological correlates to lower grip strength and startle response were reported. The startle response in all groups remained within the range for available historical control data. The eMSCA considered the effects on startle response as adverse, since these were observed in both sexes, recovered only partially, and based on the magnitude of the change.

Table 18: Startle response differences from the controls in the F1 animals: (%)

	Males			Females		
Dose (mg/kg bw/d)	**15**	**50**	**150**	**15**	**50**	**150**
PND 25						
Average response amplitude			-38**		-10	-30**
Maximum response amplitude			-32**		-11	-38**
PND 60						
Average response amplitude			-23			-4
Maximum response amplitude			-22			-15

**Wilcoxon test significant at 1%

Organ weight examination showed a reduction in the absolute brain weight at 150 mg/kg bw/day, on PND 21-22 (subset A) and PND 70-73 (subset B) (Table 19). The level of reduction of absolute brain weight was similar between Subset A and B, whilst the level of reduction in body weight of Subset B was less than half that in Subset A. This indicated that the effect on brain weight could remain at similar degrees for a prolonged period, after a partial recovery of body weights. The study authors indicate that the lower brain weights were ascribed to lower body weights and not a direct effect, since relative brain weights were higher than the control means. The authors concluded that in the absence of macroscopic or histopathological changes in the central or peripheral nervous tissues, the brain weight changes were related to effect on body weight.

No changes were noted in any of the other F1-generation (neuro-)developmental parameters, including hearing and pupillary reflex, learning and memory, gross brain dimensions and brain morphometry.

Table 19: body and brain weight differences from the controls in the F1 animals (%)

	Males			Females		
Dose (mg/kg bw/d)	**15**	**50**	**150**	**15**	**50**	**150**
Subset A: PND 21-22						
Body weight	2	2	-25**	2	2	-22**
Brain weight (fresh) Abs Rel	-1 0	2 1	-10** 27**	3 2	1 0	-6** 20**
Brain weight (fixed) Abs Rel	2 -1	6 -1	-7 27**	1 2	-3 -5	-6 29**
Subset B: PND 70-73						
Body weight	1	5	-10**	1	1	-7**
Brain weight (fresh) Abs Rel	2 4	6 7	-6 7	1 0	1 0	-5** 2
Brain weight (fixed) Abs Rel	4 0	5* -5	-3 6	2 -1	-2 -3	-5* 3

*P<0,05, ** P<0,01

The registrant(s) conclude that the effects on motor activity and grip strength were reversible and thus not adverse. Reduced startle response was considered not completely reversible. Based on the magnitude and non-reversible nature the reduced startle response was an adverse effect. Maternal NOAEL was set to 50 mg/kg bw/day, based on clinical signs and reduced weights at 150 mg/kg bw/day. Developmental NOAEL was set to 50 mg/kg bw/day, based on reduced startle response at 150 mg/kg bw/day.

The eMSCA notes that the results of the DNT study are consistent with the existing data on the substance. The observed neurotoxicity pattern suggests toxicity to the peripheral and/or central nervous system as demonstrated by changes in gait, posture, motor activity, grip strength and acoustic startle response in both adult and developing offspring. According to the OECD Guidance Document 20 (2004), grip strength is reduced by agents that produce peripheral neuropathy, whereas motor activity and startle response may be reduced by CNS depressants.

Further, the toxicity pattern suggests that the substance induces acute or sub-chronic neurotoxicity. According to the US EPA Guidance document on developmental neurotoxicity (US EPA 2016), changes in the dams may indicate sub-chronic toxicity. Effects observed in pups during the pre-weaning period may likewise reflect acute or sub-chronic toxicity. Further, changes into adulthood may be expected because of exposure during development.

The observed effects on motor activity, grip strength and acoustic startle response declined in intensity in the F1-animals, post-weaning after end of the treatment period. The effects on motor activity may be regarded as reversible, as no change was observed after PND 13 and the measured values were like the control levels, later during lactation and post-weaning. The reduced grip strength was declined in post weaning F1-animals but did not recover completely to the control levels. Also, the observed changes in the acoustic startle response were less enhanced, but still present towards the end of study period. These

changes suggest a persistent effect in the adult F1-animals because of *in-utero* and/or early postnatal exposure.

Similarly, reduction in the absolute brain weight in the F1-animals seemed to be persistent as it was detected at PND 70-73, after partial recovery of the body weights. Reduced absolute brain weight following exposure to the Substance was also reported in a 28-day study in rats. According to the US EPA Guidance, in adult animals' brain weight is highly conserved in the presence of changes in body weight. Studies of malnutrition during development suggest that severe reductions in body weight (e.g., <50% of controls) will result in lower brain weight, but this has been less studied with regards to moderate or slight (e.g., <10% of control) body weight differences. In general, effects on brain weight cannot be dismissed even in the presence of body weight differences and should be considered treatment-related and adverse (US EPA 2016).

Neurotoxic adverse effects are defined as changes in the structure or function of the central and/or peripheral nervous system, including effects that are transient and occur only at specific times during development (US EPA 2016). Thus, based on the result of the DNT study, showing adverse effects on the nervous system in the developing animals because of exposure during development, the eMSCA concluded that the Substance causes developmental neurotoxicity. However, in the eMSCA view the observed effects may not meet the criteria for classification as Repr. Category 1B for developmental toxicity.

According to the eMSCA the developmental NOAEL should be 15 mg/kg bw/day, based on changes in the startle response observed at the next dose level. Thus, the critical NOAEL for developmental neurotoxicity remains the one from the RACB study (<6.8 mg/kg bw/day). The eMSCA agrees with the maternal NOAEL=50 mg/kg bw/day.

Summary of toxicity to reproduction

The available reproductive toxicity studies show that the Substance causes adverse effect on development, specifically developmental neurotoxicity, because of pre and/or postnatal exposure to developing animals. Developmental neurotoxicity of the Substance is manifested as both functional and structural effects on the nervous system of the offspring early in life and during adulthood.

7.9.8. Hazard assessment of physico-chemical properties

Not relevant for this evaluation.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The registrant(s) identified neurotoxicity as the most sensitive endpoint to set the DNELs for long-term inhalation systemic effects and long-term dermal systemic effects.

The registrant(s) used a NOAEC of 62.5 mg/m^3 as a starting point to derive the DNEL for long-term inhalation systemic effects and applied the default assessment factors (AFs) recommended in the "ECHA Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health" (version 1, May 2008). The NOAEC of 62.5 mg/m^3 was from a 90-day inhalation study according to OECD TG 413 where rats were exposed nose-only to the Substance for 6 hours – once daily, 5 days per week for 13 weeks (Exp Key Repeated dose toxicity: inhalation.001). The exposure of workers is assumed to be 8 hours per day, and since the rats were only exposed for 6 hours per day ECHA guidance proposes a correction of the starting point to account for differences in the experimental and human exposure. The guidance further advice the use of allometric scaling to account for differences in inhalation volumes between rats and humans, by multiplying the NOAEC with a factor of 6.7/10. The registrant(s) have not performed the above-mentioned correction of the starting point. Therefore, the eMSCA has revised the DNEL by correcting the starting point.

The eMSCA does not agree with the setting of the systemic NOAEC of 62.5 mg/m^3. According to the eMSCA a NOAEC of 10 mg/m^3 from the same study should be used to derive the systemic inhalation DNEL. The eMSCA, in the subsequent step, has revised the DNEL using a NOAEC of 10 mg/m^3, correcting the starting point for differences in the experimental and human exposure, and applying the ECHA default AFs (Table 20).

For long-term inhalation local effects, the registrant(s) used a NOAEC of 10 mg/m^3 as a starting point to derive the DNEL (Exp Key Repeated dose toxicity: inhalation.001). The local NOAEC was set because of the squamous metaplasia and respiratory metaplasia in the olfactory epithelium observed at next dose levels (25 and 62.5 mg/m^3). The registrant(s) state that this is because of the release of methacrylic acid after metabolic hydrolysis of the Substance. The registrant(s) further state that human sensitivity is not more pronounced than rat sensitivity to the irritating properties of methacrylic acid derivatives in the olfactory epithelium (cf. OEL justification for methyl methacrylate, SCOEL, 2007). They, therefore, deviate from the ECHA default AFs and apply an overall AF of 4 resulting in a DNEL of 2.5 mg/m^3 for long-term inhalation local effects.

The registrant(s) used a NOAEL of 9.1 mg/kg bw/day from a 12-month oral repeated dose toxicity study in rats as a starting point to derive the DNEL for long-term dermal systemic effects (Exp Key Repeated dose toxicity: oral.001). When deriving the DNEL the registrant(s) deviated from the ECHA default AFs. Instead of applying the default AF of 5 for intraspecies differences, the registrant(s) applied an AF of 3 with the justification that the "known mode of action involving ubiquitous and non-specific enzyme systems (carboxylesterases, tricarboxylic acid cycle) makes a lower variability likely, hence the AF of 3 by ECETOC (2010) is sufficiently conservative for workers". The registrant(s) did not apply the default AF of 2.5 for remaining interspecies differences either, with the justification that "the substances are metabolised via general metabolic pathways that are common and very similar to rodents and humans and the absence of any specific target organs indicating a specific MOA at high concentrations there is no reason to believe that an additional AF of 2.5 for remaining differences is justified". However, there are no toxicokinetic studies in the registration dossier(s) in support of this hypothesis. One in vitro study on the metabolism of the Substance in the registration dossier(s) demonstrates 2-fold increase in the reaction rate after phenobarbital induction that suggests a cytochrome P-450 dependent metabolism. The neurotoxicity of the Substance in adult experimental animals is well established. However, there is no information in the registration dossier(s) describing the mode of action for neurotoxicity. Therefore, in the eMSCA's opinion, the justification for deviating from the default AFs provided by the registrant(s) is not backed by sound substance-specific information. The eMSCA has therefore revised the DNEL by applying the default AFs. Furthermore, ECHA (2012) advice against using default AFs other than those recommended by ECHA.

Because of the statistically significant reduction in the hindlimb grip strength during week 3 even in the low-dose F1 animals, it was concluded in the OECD SIDS (2002) evaluation for the Substance that the NOAEL for developmental toxicity is less than 6.8 mg/kg bw/day in the RACB study (Exp Key Developmental toxicity / teratogenicity.001). The eMSCA agrees with the OECD SIDS conclusion and has therefore revised the DNEL by using the LOAEL of 6.8 mg/kg bw/day, and by applying the ECHA default AFs (Table 21).

The same DNEL values were set by the registrant(s) for acute systemic effects as for the long-term systemic effects for both dermal and inhalation exposure.

In the SEv decision a justification for deviating from the default assessment factors for derivation of the DNEL for the dermal long-term systemic effects was requested. DNEL derivations were updated in the registration(s) in 2021. According to the updated information in the CSR, in the absence of a relevant dermal study, three studies via other routes: Two chronic oral studies in rats and mice (Klimisch 2) and a subchronic guideline study in rats with inhalative exposure (Klimisch 1) were used for derivation of dermal DNEL. The DNEL calculations provided a consistent DNEL range between 1.00 and 1.11 mg/kg bw/d. Based on data from two different routes of exposure and different species, it was concluded that the selected lowest DNEL ensures a sufficiently safe level for workers.

The eMSCA notes that the DNELs derived by the registrant(s) for the long-term dermal systemic effects are higher than the DNELs calculated by the eMSCA.

Table 20

CRITICAL INHALATION DNELS FOR WORKERS BY THE EMSCA					
Endpoint of concern	**Type of effect**	**Critical studies**	**Corrected dose descriptor(s)**	**DNEL**	**Justification/ Remarks**
Systemic toxicity	Long-term inhalation – systemic effects	90-day inhalation study in rats according to OECD TG 413 (Exp Key Repeated dose toxicity: inhalation.001)	NOAEC: 31.40625 mg/m^3 Corrected from NOAEC: 62.5 mg/m^3 because of the differences between experimental and human exposure conditions – a factor of 0.75 (6 h/d / 8 h/d) and a factor of 0.67 (6.7 m^3 / 10 m^3).	1.25625 mg/m^3	Default AFs from ECHA guidance (2012). Overall AF: 25 (Interspecies, remaining differences: 2.5, intraspecies: 5, exposure duration: 2)
Systemic toxicity	Long-term inhalation – local effects	90-day inhalation study in rats according to OECD TG 413 (Exp Key Repeated dose toxicity: inhalation.001)	NOAEC: 7.5 mg/m^3 Corrected from NOAEC: 10 mg/m^3 because of differences between experimental and human exposure conditions (only a factor of 0.75; the factor of 0.67 to account for differences in respiratory volume doesn't apply to local effects.	0.3 mg/m^3	Default AFs from ECHA guidance (2012). Overall AF: 25 (Interspecies, remaining differences: 2.5, intraspecies: 5, exposure duration: 2)

Table 21

CRITICAL DERMAL DNELS FOR WORKERS BY THE EMSCA					
Endpoint of concern	**Type of effect**	**Critical studies**	**Corrected dose descriptor(s)**	**DNEL**	**Justification/ Remarks**
Neurotoxicity	Long-term dermal – local effects	12-month oral study in rats (Exp Key Repeated dose toxicity: oral.001)	NOAEL: 9.1 mg/kg bw/day	0.182 mg/kg bw/day	Default AFs from ECHA guidance (2012). Overall AF: 50 (Allometric scaling rat to human: 4, interspecies, remaining differences: 2.5, intraspecies: 5)
Developmental neurotoxicity	Long-term dermal – systemic effects	The RACB study (Exp Key Developmental toxicity / teratogenicity.001)	LOAEL: 6.8 mg/kg bw/day	0.045 mg/kg bw/day	Default AFs from ECHA guidance (2012). Overall AF: 150 (LOAEL as dose descriptor: 3, allometric scaling rat to human: 4, interspecies, remaining differences: 2.5, intraspecies: 5)

7.9.10 Conclusion of the human health hazard assessment and related classification and labelling

The Substance is self-classified as STOT SE, Category 2, H371 and STOT RE Category 2, H373 for toxicity to the nervous system.

Further, the available developmental neurotoxicity data show that the Substance causes toxicity to the developing nervous system. The eMSCA is of the view that the observed developmental neurotoxicity effects may not meet the criteria for classification of the substance as Repr. Category 1B for development.

The eMSCA may perform a RMOA to conclude on the appropriate regulatory risk management option for the Substance, including the need for harmonised classification for the neurotoxic effects.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Not relevant for this evaluation.

7.12. Exposure assessment

The registrant(s) generated exposure scenarios and made exposure estimations for manufacture and for all the identified uses of the Substance given below using EasyTra 3.5 and 4.0 models[4].

1. Manufacture of substance
2. Intermediate: synthesis of derivatives at industrial site
3. Formulation and repacking of preparations – Industrial
4. Use in emulsion polymerisation – Industrial
5. Use in silk weighting – Industrial
6. Use in reactive resins – Industrial
7. Use in reactive resins – Professional

7.12.1. Human health

7.12.1.1. Worker

See section 7.13.

7.12.1.2. Consumer

In the registration dossier(s) no consumer use was identified.

7.12.2. Environment

Not relevant for this evaluation.

7.12.3. Combined exposure assessment

Not assessed in the registration dossier(s) or by the eMSCA.

7.13. Risk characterisation

The registrant(s) provided an updated EasyTRA (EasyTRA 5.0.0) risk assessment report in 2021. The report contains estimated exposures for different exposure scenarios for human health and the environment.

In this report, risk assessment for worker exposure on the Tier 1 and Tier 2 levels were performed. The exposure was calculated by the standard entry values for the inhalation and dermal routes. The calculated exposure level was set in relation to the inhalation and dermal reference values to calculate the "Risk Characterization Ratio" (RCR). The RCRs for exposure via both routes was also calculated.

The eMSCA concludes that no further information request under SEv is needed.

[4] http://easytra.com/, last accessed 31 October 2016.

7.14. References

Note: The references citing the studies reported in the registration dossier(s) can be found on the ECHA dissemination webpage http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

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European Commission. 2006. *Recommendation from the Scientific Committee on Occupational Exposure Limits for methyl methacrylate*. SCOEL/SUM/126

Tanii, H., Hashimoto, K. 1985. *Mutagenicity of acrylamide and its analogues in Salmonella typhimurium*. Elsevier, Mutation Research, 158: 129-133

US EPA 2016. DEVELOPMENTAL NEUROTOXICITY STUDY (DNT) GUIDANCE DOCUMENT

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7.15. Abbreviations

AF	Assessment Factor
ALD50	Approximate Lethal Dose 50
CCH	Compliance Check
CoRAP	Community Rolling Action Plan
DNEL	Derived No Effect Level
DNT	Developmental Neurotoxicity
EC3	Effect Concentration 3; the amount that produces a Stimulation Index of 3
ECHA	European Chemicals Agency
eMSCA	Evaluating Member State Competent Authority
GLP	Good Laboratory Practice
LC50	Lethal Concentration 50
LD50	Lethal Dose 50
LDLo	Lowest Lethal Dose
LLNA	Local Lymph Node Assay
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
RACB	Reproductive Assessment by Continuous Breeding (protocol)
RCR	Risk Characterisation Ratio
RMOA	Risk management Option Analysis
TCLo	Lowest published Toxic Concentration