SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Butyl acrylate

EC No 205-480-7

CAS No 141-32-2

Evaluating Member State: Sweden

Dated: 9 December 2019

Template Version 2.1
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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on: 15 July 2015.

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

Butyl acrylate was originally selected for substance evaluation in order to clarify concerns about:

- Human health/reproductive and developmental toxicity
- Occupational exposure
- Aggregated tonnage

During the evaluation also other concerns were identified. The additional concerns were:

- Mutagenicity
- Derivation of DNELs

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Not applicable.

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	X

4. FOLLOW-UP AT EU LEVEL

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

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	X
Actions by the registrants to ensure safety, as reflected in the registration dossiers	

An Extended One-Generation Reproductive Toxicity Study and a Prenatal Developmental Toxicity study was performed by the Registrant(s), according to the substance evaluation decision. Provided data indicated no hazard for reproductive toxicity (fertility and development). To address the mutagenicity concern, an *in vitro* Mammalian Cell Gene Mutation assay was performed, which showed negative results. Further, the Registrant(s) provided an updated grouping justification for their proposed acrylic acid and esters category. Genotoxicity data for the category substances was considered in a Weight-of-Evidence (WoE) approach to conclude on the genotoxicity potential. The evaluating MSCA concluded, based on the WoE analysis of the available data, including that from other acrylate category substances that there is no longer a concern for mutagenicity for butyl acrylate which needs to be further addressed under this substance evaluation and that no further genotoxicity testing was needed.

In addition, the Registrant(s) updated the CSR with further risk management measures and indication of "uses advised against". Use of gloves to prevent any skin contact was indicated. No professional worker or consumer use of the substance is supported with the reasoning that butyl acrylate is a highly reactive substance and should only be used under controlled conditions in industrial settings (latest update of the lead registration April 2019).

5.2. Other actions

Not applicable.

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

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Butyl acrylate was originally selected for substance evaluation in order to clarify concerns about:

- Human health/reproductive and developmental toxicity
- Occupational exposure
- Aggregated tonnage

During the evaluation also other concerns were identified. The additional concerns were:

- Mutagenicity
- Derivation of DNELs

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Reproductive toxicity	An Extended One-Generation Reproductive Toxicity Study (EOGRTS) was performed according to the SEV decision. No reproductive toxicity (effects on fertility or sexual function) was observed / No further action.
Developmental toxicity	A Prenatal Developmental Toxicity (PNDT) study was performed according to the SEV decision. No developmental toxicity was observed / No further action.
Genotoxicity	An *in vitro* Mammalian Cell Gene Mutation assay was performed following the SEv decision, which showed negative results. Based on this result and WoE assessment of other data submitted following the SEv decision and outcome of assessments of genotoxicity of acrylates performed by other regulatory bodies, the eMSCA concludes that there is no longer a concern for mutagenicity which needs to be further addressed under this SEv / No further action.
Occupational exposure	Exposure scenarios for the industrial worker were updated in the registration(s). Professional worker uses (of the monomer) were advised against / No further action.
DNEL derivation (Industrial worker)	Information on derivation of dermal DNELs was requested in the SEv decision. CSR was updated with a qualitative assessment of the dermal DNELs. Recommendation for use of gloves to avoid skin sensitisation was included in the registration(s) / No further action.

7.2. Procedure

Butyl acrylate was included in the Community Rolling Action Plan (CoRAP) for substance evaluation in 2013 by the competent authority of Sweden. The scope of the evaluation was human health, targeted to concerns for reproductive toxicity (fertility and development), mutagenicity, DNEL derivation and occupational exposure.

A substance evaluation decision was issued on 15 July 2015, with request for information on reproductive toxicity, prenatal developmental toxicity, genotoxicity (mammalian cell gene mutation and cytogenicity) and DNEL derivation.

In October 2017 the registration(s) were updated. An Extended One-Generation Reproductive Toxicity Study (OECD TG 443), a Prenatal Developmental Toxicity Study (OECD TG 414) and an *in vitro* Mammalian Cell Gene Mutation Assay (OECD TG 490) were provided. The CSR was updated to address the concerns related to DNEL derivation. Also, an updated grouping justification for the Acrylate category was provided.

The evaluating MSCA assessed the new information in the follow-up evaluation and concluded that no further testing was needed for reproductive toxicity (fertility and development). No further genotoxicity testing was requested, based on the available information on butyl acrylate and other acrylate category substances.

The evaluating MSCA has also taken into account the outcome of other assessments of butyl acrylate and its analogue short chain (methyl, ethyl and ethylhexyl) acrylates, performed by other regulatory bodies/programs. These include the Canadian screening assessment programme (Health Canada, 2017), the OECD High Production Volume programme (OECD SIDS 2002, 2003 and 2004), European Chemicals Bureau (EU RAR, 2002 and 2005), International Agency for Research on Cancer (IARC, 1999 and 2003) and National Toxicology Program (NTP 1986, 2000). Overall, these assessments conclude on absence of carcinogenic, mutagenic or reprotoxic (CMR) properties for these short-chain acrylates.

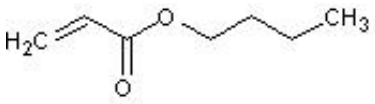
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Butyl acrylate
EC number:	205-480-7
CAS number:	141-32-2
Index number in Annex VI of the CLP Regulation:	607-062-00-3
Molecular formula:	C7O12H2
Molecular weight range:	128,17 g/mol
Synonyms:	n-Butyl acrylate Butyl 2-propenoate

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

Structural formula:



7.3.1. Grouping and read-across

In the registration(s) a justification document for the "Acrylate category" is provided (October 2017). The Registrants define the category as a group of structurally related substances, consisting of acrylic acid and its esters, with different chain length/configuration:

- acrylic acid (CAS No. 79-10-7)
- methyl acrylate (CAS No. 96-33-3)
- ethyl acrylate (CAS No. 140-88-5)
- butyl acrylate (CAS No. 141-32-2)
- isobutyl acrylate (CAS No. 106-63-8)
- tert-butyl acrylate (CAS No. 1663-39-4)
- 2-ethylhexyl acrylate (CAS No. 103-11-7)

During the initial evaluation under SEv the Registrant(s) proposed read-across between butyl acrylate and these category substances to conclude on the mutagenicity and reproductive toxicity endpoints. However at that time the provided read-across justification did not fulfil the requirements, as defined in Annex XI of the REACH regulation and was considered not sufficient to conclude on potential mutagenicity and reproductive toxicity. Further information was requested in a SEv decision[2] in 2015. Following that decision, the Registrant(s) updated the grouping justification in 2017. In the updated justification, the category proposed by the Registrants is based on:

- structural similarity
- common breakdown products and
- similar physico-chemical properties and human health and environmental toxicity

All substances in the category have the acrylic group as the functional group. Physio-chemical properties show a constant pattern with increasing chain length. Read-across is further based on hydrolysis of these acrylates to acrylic acid. The substances in the group are rapidly absorbed and metabolised to acrylic acid and corresponding alcohols (Roos, 2015). Studies in rats show that following oral administration and absorption butyl acrylate is mainly hydrolysed by carboxy esterase to acrylic acid and butanol and ultimately eliminated as CO_2. A minor portion (ca. 10%) is conjugated to gluthatione and excreted in urine (Sanders et al., 1988).

Data on the human health toxicity further supports the read-across. In summary, the most prominent effect of acrylates on human health seems to be irritation. Acrylic acid is corrosive to skin and eyes. All acrylate esters in the category are strong to moderate skin irritants. The severity of irritation decreases with the increase of the acryl chain length. Repeated dose toxicity studies, ranging from 28-days to 2-year, show similar effects in rats and mice, exposed via inhalation or the oral route. The toxicity profile in these studies seems to be dominated by local irritation, irrespective of the exposure route. Liver, kidneys, respiratory organs and stomach are identified as the target organs. Tubular degeneration in the kidney and hyperkeratosis in the stomach (following gavage administration), due to the irritative properties, is reported. In the inhalation studies irritation of the olphactory epithelium is observed.

[2] https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e5fca

Regarding the genotoxicity potential, all substances in the category show negative results in the Ames test. Positive results in the *in vitro* mammalian cell gene mutation assays and *in vitro* chromosome aberration results (mostly at cytotoxic doses) is reported, but not confirmed *in vivo*. Also, based on rapid metabolism of these acrylates, limited concern is expected *in vivo* considering absence of mutagenic potential for acrylic acid and the corresponding alcohols. Accordingly, the available chronic studies indicate no carcinogenic properties via a genotoxic Mode-of-Action for these substances. Carcinogenicity tests are available for acrylic acid and several of the acrylate esters via different administration routes. Ethyl acrylate, given via gavage was carcinogenic in the forestomach in rats (Smith et al., 1986). The tumor formation was suggested to be a result of the lesions induced locally, which during the healing process lead to epithelial proliferation (Butterworth, 1989; Ghanayem et al., 1986). No evidence of carcinogenicity was observed in rats or mice in inhalation, dermal exposure or drinking water studies with ethyl acrylate (Bernacki et. al., 1987a and b; Miller et al., 1985; Nylander-French and French 1998; IARC 2003). Butyl acrylate was not carcinogenic in a 2-year inhalation study in rats up to the highest tested dose (135 ppm) and in a lifetime skin painting study in mice (Reininghaus et al., 1991, Unpublished report, 1982).

The evaluating MSCA concluded that the proposed grouping and read across approach is supported by the provided data and acceptable for assessing potential mutagenicity of butyl acrylate.

Table 6

SUBSTANCE IDENTITY (Analogue substance)	
Public name:	Methyl acrylate
EC number:	202-500-6
CAS number:	96-33-3
Index number in Annex VI of the CLP Regulation:	607-034-00-0
Molecular formula:	C4H6O2
Molecular weight range:	86 g/mol
Synonyms:	Methyl 2-propanoate Methyl acrylic ester

Type of substance: mono constituent

Structural formula:

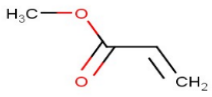


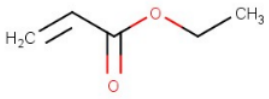
Table 7

SUBSTANCE IDENTITY (Analogue substance)	
Public name:	Ethyl acrylate
EC number:	205-438-8
CAS number:	140-88-5
Index number in Annex VI of the CLP Regulation:	607-032-00-X

Molecular formula:	C5H8O2
Molecular weight range:	100 g/mol
Synonyms:	Ethyl propanoate Ethyl 2-Propenoate

Type of substance: mono constituent

Structural formula:



7.4. Physico-chemical properties

Table 8

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	5hPa at 22°C
Water solubility	1,7g/L at 20°C
Partition coefficient n-octanol/water (Log Kow)	2,38 at 25°C
Flammability	Flammable upon ignition. Has no pyrophoric properties and does not liberate flammable gases on contact with water. Not a self-heating substance or mixture.
Explosive properties	Non explosive
Oxidising properties	No oxidising properties
Granulometry	Not applicable
Stability in organic solvents and identity of relevant degradation products	Not applicable
Dissociation constant	Not applicable

7.5. Manufacture and uses

7.5.1. Quantities

Table 9

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 9

USES	
Uses as intermediate	Monomer in polymers
Formulation	Use in laboratories Manufacture and distribution of the substances Formulation of coatings with a polymer which contains the substance as a monomer Formulation of pre-polymer mixtures
Uses at industrial sites	Use of intermediates Polymerisation at production sites Polymerisation at downstream user sites Formulation Monomer
Uses by professional workers	Application of coatings Use of ink and ink components Indoor/oudoor application of adhesives
Consumer Uses	Indoor/oudoor application of adhesives Use of ink and ink components
Article service life	Use of ink and ink components

Information was collected from the ECHA dissemination site on 2019-02-22.

See also section 6.12.1.2.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 10

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
607-062-00-3	*n*-butyl acrylate	205-480-7	141-32-2	Flam. Liq. 3 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1 STOT SE 3	H226 H315 H319 H317 H335		

7.6.2. Self-classification

- In the registration(s):
  Acute Tox. 4 H332

Aquatic Chronic 3 H412

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Not evaluated. Studies in rats show that following oral administration butyl acrylate is mainly hydrolysed by carboxy esterase to acrylic acid and butanol and ultimately eliminated as CO_2. A minor portion (ca. 10%) is conjugated to gluthatione and excreted in urine (Sanders et al., 1988).

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated.

7.9.3. Sensitisation

Not evaluated. The substance has a harmonised classification as Skin Sens. 1.

7.9.4. Repeated dose toxicity

Not evaluated.

7.9.5. Mutagenicity

During the SEV a concern for mutagenic potential of butyl acrylate was identified, based on positive *in vitro* and inconclusive *in vivo* cytogenicity data. Also, a data gap for an *in vitro* Mammalian Cell Gene Mutation test was identified.

7.9.5.1. Gene mutation

The *in vitro* gene mutation studies in bacteria with butyl acrylate are negative. At the time of the initial evaluation, no *in vitro* Mammalian Cell Gene Mutation study was available. Instead, read across to studies with ethyl acrylate was proposed, that showed both negative and positive result. However, the read-across was rejected based on insufficient justification. To address the potential for inducing gene mutation in mammalian cells an *in vitro* Mammalian Cell Gene Mutation test (OECD TG 490) was conducted. The assay was performed in the Mouse Lymphoma Cells, with and without metabolic activation. Cells were exposed to butyl acrylate at concentrations up to 900 ug/ml. Cytotoxicity about or below 20% was observed at the high dose. In all experiments, mutation frequencies were close to or within the respective vehicle control. Thus, under tested conditions butyl acrylate did not induce mutations *in vitro*.

7.9.5.2. Clastogenicity

During the SEv *in vitro* Mammalian Cell Chromosome Aberration test and Micronucleus tests in mammalian cells with butyl acrylate were available. These tests were considered unreliable because of the inadequate number of cells and/or doses tested.

In vivo cytogenicity (chromosome aberration) assays with butyl acrylate were also available (Engelhardt and Klimisch, 1983). However, these studies were regarded as limited and thus insufficient to conclude on the mutagenicity potential. The two *in vivo* chromosome aberration tests with butyl acrylate were done in rat and hamster, exposed via inhalation for 4 days. The results of these studies did not indicate any chromosome damaging effects. However, the studies had the following limitations: only one dose was tested, exposure was repeated, positive controls were missing and sampling time was too short post exposure.

A tiered testing strategy was requested in the SEv decision[3]. Testing of the chromosome damaging potential by *in vitro* Mammalian Micronucleus test (OECD TG 487) was requested as the initial step. Depending on the outcome, further *in vivo* testing was requested. As an alternative, the Registrant(s) were requested to provide information for re-evaluation of the reliability of the existing *in vivo* chromosome aberration study.

The Registrant(s) did not follow the requested tiered testing strategy. Instead, they provided information on the existing *in vivo* cytogenicity data. Concerning the dose selection, they indicated that the tested doses were about 1/3 of the LC_{50} values. Severe general toxicity was observed, indicating systemic availability and that an MTD was achieved. Regarding the sampling time, killing animals 5 hours after the last exposure allowed the analysis of several post-exposure duration periods. Regarding lack of positive controls, the Registrant(s) compiled data from the studies performed during this period in the same laboratory to verify the proficiency of the laboratory. Regarding the tested dose level, the evaluating MSCA notes that a MTD seems to have been reached, based on the clinical observations. In regard to the sampling time, 12-18 hours (corresponding to 1,5 cell cycles) after the last treatment, before collecting the cells is recommended (OECD TG 475). Sampling after a too short time (in this study 5 h) may not be enough for detection of aberrations. On the other hand, since cells with abberations may be lost after the first cell division, a too long sampling time could also result in a false negative response. Therefore, to be able to detect effects, it is crucial to perform the sampling within the recommended window of time. Regarding the information provided to compensate for the lack of concurrent positive controls the eMSCA notes that the compiled information included only one positive *in vivo*, inhalation chromosome aberration test, in a 14 year time period (1975-1989). Thus, the proficiency of the laboratory remains uncertain. Because of the remaining uncertainties described above, the evaluating MSCA considered the study inconclusive.

In the updated registration(s) also a revised Weight-of-Evidence (WoE) approach was performed to conclude on the mutagenicity potential. Genotoxicity data on butyl acrylate and the other acrylate category substances were considered (see section 7.3.1. for read-across basis). The Registrant(s) concluded that overall there is no concern for mutagenicity of this group of substances based on the following:

- Acrylic acid did not induce gene mutations *in vitro* in mammalian cells in a HPRT assay, but was positive in a mouse lymphoma cell TK-gene mutation assay and in an *in vitro* chromosomal aberration test (Moore et al., 1988 and 1999). In the positive mouse lymphoma assay mainly small colonies were formed, indicating a mutagenic potential due to clastogenicity. *In vivo*, acrylic acid was not mutagenic in a chromosome aberrartion test and a dominant lethal assay (McCarthy et al., 1992).
- Methyl acrylate was negative in an HPRT gene mutation assay, but was positive in a mouse lymphoma cell TK-gene mutation assay in the absence of metabolic activation (Moore et al., 1988 and 1989). Positive results were observed at cytotoxic concentrations (≤ 50% cell survival) and the majority of the mutant

[3] [3] https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e5fca

colonies were small, suggesting a clastogenic mechanism *in vitro*. *In vivo*, methyl acrylate was negative in mouse micronucleus assay (Hachiya et al., 1981).

- For ethyl acrylate, similar results were observed; negative HPRT assay, positive mouse lymphoma TK-gene mutation assay with small mutant colonies (Moore et al., 1988 and 1989) and negative *in vivo* mouse micronucleus assays and chromosome aberration tests (Kligerman et al., 1991; Ashby et al., 1989). Ethyl acrylate was negative in an *in vivo* gene mutation assay in gpt Delta Mice (Unpublished data 2015).
- Butyl acrylate was negative in an mouse lymphoma cell TK-gene gene mutation assay and in an *in vitro* Unschedueled DNA Syntheses assay (Unpublished data, 2016; Wiegand et al., 1989). *In vivo*, butyl acrylate showed no genotoxic effects after inhalation exposure in a chromosome aberration assay, with limitations (described above).
- The negative results of the long-term carcinogenicity studies with acrylates was also considered to add to the weight of evidence for lack of genotoxicity.

The evaluating MSCA considers the existing genotoxicity information on butyl acrylate, by itself not conclusive on the clastogenicity potential. However, based on the WoE analysis of the currently available data there is no longer a concern for mutagenicity that needs to be further addressed under this SEv. This conclusion is based on the current knowledge, considering also the available data on the acrylate category substances and by taking into account the outcome of other existing assessments (see section 7.2). Therefore, no further genotoxicity testing is needed under this SEv.

7.9.6. Carcinogenicity

Not evaluated.

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

A concern for reproductive toxicity of butyl acrylate was identified, based on lack of information (data gap) on possible effects on sexual function, fertility and development. Subsequent to the requests in the SEv decision, the Registrant(s) updated the registration(s) with an EOGRTS (OECD TG 443) and a PNDT study (OECD TG 414) to address the concern.

7.9.7.1. Fertility

Initially, a range finding reproductive toxicity study was performed, with doses 0, 40, 160 and 400 mg/kg bw/day. Animals at the highest dose showed salivation and red material around the eyes, nose and mouth. These effects were observed to a lesser extent at the mid-dose. Males were more affected. Macroscopic examinations showed thickened and eroded stomach in the 400 mg/kg/day group males. Thickened stomach was also observed at 160 mg/kg bw/day. No systemic or reproductive toxicity was observed.

In the actual EOGRTS performed via gavage, dose levels of 20, 50 and 150 mg/kg bw/day were selected (Unpublished data, 2017a). The high-dose was expected to induce some parental toxicity. In the first parental generation (P) test substance-related gross observations were reported at 150 mg/kg bw/day. Thickened stomach occurred in 3 of 30 males. Microscopic findings were in the nonglandular stomach, liver and kidneys. Nonglandular stomach findings were minimal to moderate epithelial hyperplasia and hyperkeratosis. The hyperplasia was characterized by increased thickness (increased number of cell layers) of the squamous epithelium with an increased thickness of the keratinized outer layers of the epithelium (hyperkeratosis). At 150 mg/kg bw/day minimal edema and congestion was observed in the submucosa adjacent to the hyperplasia and hyperkeratosis in one female. The observed hyperplasia and/or hyperkeratosis in the F0 generation were considered adaptive but adverse. In the F1 animals thickened stomach was observed at 20, 50 and 150 mg/kg bw/day males and

females in Cohort 1A. At necropsies, thickened stomachs were noted in the 50 and 150 mg/kg bw/day. Test substance-related microscopic changes were observed in the nonglandular stomach in F1 males and females at all doses. Hyperkeratosis was observed in all treated animals, while epithelial hyperplasia was observed at 50 and 150 mg/kg bw/day. These findings were not associated with clinical pathology changes, but slightly less severe when compared to the F0 generation and were considered adverse at 150 mg/kg bw/day.

The evaluating MSCA concluded that butyl acrylate does not cause reproductive toxicity up to doses that cause irritation and thus are feasible to test.

7.9.7.2. Developmental toxicity

Several Prenatal Developmental Toxicity (PNDT) studies with butyl acrylate in rats and mice are available. In the initial SEV a concern for developmental toxicity was identified, based on increased incident of resorptions in one rat study (Merkle and Klimisch, 1983). In addition, a data gap for developmental toxicity was identified as PNDT studies in two species, (one of which a non-rodent) was required according to the REACH Annex X, 8.7.2.

A PNDT study in rabbit was requested in the SEV decision. For this study doses were selected based on a previous range-finding study in which rabbits were dosed 50, 125, 250 and 400 mg/kg bw/day. Lower mean body weight gains (approximately 18%) and food consumption combined with decreased defecation was noted at 400 mg/kg bw/day throughout the treatment period. No significant clinical observations or treatment-related findings were reported at any dose. The doses selected for the actual study were 400 mg/kg bw/day as the high-dose, as it was expected to produce some maternal toxicity (i.e., decreased body weight gain), 150 and 50 mg/kg bw/day (Unpublished data, 2017b). No effects were observed on body or organ weights. The numbers of fetuses (litters) were 219(25), 214(24), 199(25) and 214(24) in the control, 50, 150 and 400 mg/kg bw/day groups, respectively. Malformations observed in 2(1), 4(4), 5(4) and 0(0) fetuses (litters) in the same respective treatment groups were considered spontaneous in origin.

The evaluating MSCA concluded that there was no remaining concern for developmental toxicity.

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated.

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

7.9.9.1. Worker

7.9.9.1.1. Local effects

Long-term inhalation DNELs

The EU Scientific Committee on Occupational Exposure Limits (SCOEL) recommended an 8 hour OEL Time-Weighted-Average (TWA) of 2 ppm (11 mg/m^3) for butyl acrylate in 1993. This recommended OEL is used as DNEL, as it is based on evaluation of health effects. The SCOEL decision was based on a 2 year inhalation study with butyl acrylate (Reininghaus et al., 1991). The critical effect was atrophy of the olfactory epithelium. In this study, rats were exposed to 15, 45 and 135 ppm (80, 240 and 720 mg/m^3). Dose-related changes were observed in the olfactory epithelium and cornea, with minimal effects in a few animals at the lowest dose and almost all animals affected at the high dose. Changes in the eyes were non-significant at the low and middle dose. No treatment-related tumours were reported. The study LOAEL of 15 ppm (80 mg/m^3) for

atrophy of the olfactory epithelium in rats, was considered to be the best available basis for proposing occupational exposure limits. SCOEL considered an uncertainty factor of 5 to allow for the absence of a NOAEL and of reliable human data. Taking into account the preferred value approach, the recommended 8-hour TWA is 2 ppm (11 mg/m^3). A STEL (15 min) of 10 ppm (53 mg/m^3) was proposed to limit peaks of exposure which could result in irritation.

Also, the German MAK commission has evaluated butyl acrylate with a comparable conclusion (2017). They also identified the local irritation of the olfactory epithelium of the nasal mucous membranes as the most critical effect, occurring even in the lowest concentration tested (15 ppm). According to MAK the database is suitable for estimating the no observed adverse effect concentration from the dose-response relationship according to the benchmark concept. The most sensitive relevant end point is seen as the loss of olfactory and ciliated cells and hyperplasia of the reverse cells after exposure for 24 months. For this effect a benchmark concentration of 2.8 ppm has been established for female animals and 2.7 ppm for males. Taking into consideration the reversibility of these findings in some cases the MAK value for butyl acrylate was set at 2 ppm. MAK also assumed that due to the particular nasal anatomy and respiratory physiology of the rat, a higher tissue dose is attained in the olfactory epithelium of the rat than in man. It was therefore expected that man does not react more sensitively than the rat and the burden in man under the same exposure conditions is more likely to be overestimated.

Short-term inhalation DNELs

Butyl acrylate is of medium local toxicity after short-term inhalation. It is classified for respiratory irritation after acute inhalation exposure. Based on local effects on skin, eyes and respiratory tract the substance is allocated to the moderate hazard band (H315, H319, H335). The acute local toxicity can be expected to be covered by the long term inhalation DNEL for local effects, which is the most sensitive endpoint with regards to the respiratory irritation.

Short-term and long-term dermal DNELs

The substance is irritating to the skin and causes skin sensitization in experimental animals (EC3 value was 11% w/v) of weak potency (ECETOC 2003). For these local effects, a qualitative assessment is provided in the CSR(s). Use of gloves and stringent risk management measures as outlined in ECHA guidance is required to prevent any skin contact with the substance and thus skin irritation and sensitization.

7.9.9.1.2. Systemic effects

Inhalation DNELs

No DNELs for short-term or long-term inhalation systemic effcts was derived. Systemic toxicity of butyl acrylate is considered to be covered by the long term inhalation DNEL for local effects. Butyl acrylate showed no evidence of systemic effect or carcinogenicity in a 2-year inhalation study in rats treated up to 135 ppm. It should be noted that the dose selection for the long-term studies was limited, due to the irritative potential leading to severe local effects on the upper respiratory tract.

Dermal DNELs

Butyl acrylate is of low toxicity after short term skin contact. The LD_{50} values ranged between 2000-3024 mg/kg bw. It is not classified for dermal toxicity. Therefore, no acute systemic dermal DNEL was derived. The substance caused no systemic toxicity and was not carcinogenic, when applied to the skin of mice throughout their lifetime at 1%, corresponding to about 8 mg/kg bw/d. Therefore, no DNEL for long-term systemic effects was derived. In the CSR use of gloves and of stringent risk management measures is recommended to protect from any short-term and long-term systemic dermal effects.

7.9.9.2. Consumer

Butyl acrylate per se is not intended for consumer use. However, end-use consumer products may contain trace amounts of acrylic acid and its esters as residuals (<0,1%). As a consequence, consumer exposure to acrylate monomers including butyl acrylate can be considered as very low or negligible. Therefore, no DNELs for systemic effects for the general population were derived.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Butyl acrylate has irritating and skin sensitising properties and is accordingly classified in the CLP regulation (see section 7.6).

In the repeated dose toxicity studies, local effects caused by irritation are predominant, which is also covered by current classification in the CLP Regulation.

Based on the evaluated available information, no further classification for human health is warranted.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

Sufficient data is not available to conclude on potential endocrine disturbing properties. However, no concern for ED properties was identified based on the available data.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

The exposure assessment in the registration(s) is indicated to cover the life cycle of the substance (monomer) until the trans-esterification or polymerization reaction. The unreacted, residual monomer in a polymer is to be regarded as impurity (<0,1%). Use descriptors relevant for the pure substance are addressed in the CSR.

No exposure measurements are available. Exposure estimation by modelling, using EasyTRA, version 4.1.0 is provided. The following overall exposure scenarios for industrial workers have been described:

1. Manufacture and distribution of the substance
2. Polymerization at production sites
3. Polymerization at downstream user sites
4. Manufacture of intermediates at downstream user sites
5. Use as a laboratory agent

7.12.1.1. Worker

Exposure of industrial workers to butyl acrylate via the inhalation and dermal route is expected. The Registrant(s) have provided risk assessment for local effects after long-term inhalation and dermal exposure. Peak exposure is considered not relevant for the identified uses. The occupational conditions (OCs) and risk management measures (RMMs) which have been implemented to control long term exposure are considered sufficient to control acute/short term exposure.

Due to its skin, eye and respiratory irritating properties and the skin sensitizing potential, the substance has been assigned to the "moderate hazard category". The PROC-specific OCs and RMMs, in the CSR describing the exposure scenarios, have been selected in line with the recommendations given in the ECHA Guidance on IR&CSR, Part E for this category. If the manufacturer/user complies with these conditions, the likelihood of effects due to the irritating and sensitizing potential of the substance is minimised.

As systemic toxicity of the substance after repeated administration (inhalation and dermal) seems limited and local effects predominant, DNELs derived for local effects are considered to provide an appropriate protection for any systemic effect.

In the SEV decision, ECHA requested the Registrant(s) to provide an improved qualitative assessment to demonstrate that the likelihood of skin sensitisation is avoided. The Registrant(s) updated the CSR (October 2017). It was stated that the substance is irritating to the skin and causes skin sensitisation. Therefore, use of gloves and stringent risk management measures, as outlined in ECHA guidance document: Risk characterisation (table E3-1), to protect any skin contact is required.

7.12.1.2. Consumer

Butyl acrylate is not intended for consumer use. However, end-use consumer products may contain trace levels of acrylic acid and its esters as residuals (<0,1%), due to the polymerization process. Thus, consumer exposure to acrylate monomers is considered as very low or negligible. Therefore, no RCRs were calculated for the general population.

On the ECHA dissemination site consumer uses for butyl acrylate are indicated. During the follow-up SEv and during finalizing this report the evaluating MSCA had informal contact with the Registrant(s) to clarify possibility of professional worker and consumer use/exposure. The Registrant(s) informed that the lead registration's CSR was updated (April 2019) with "uses advised against". The included uses advised against are professional worker uses in coatings, inks and adhesives. The use advised against refers to the substance as such or in a mixture, but not to the polymerized follow up product". The reason is that butyl acrylate is a highly reactive substance and should only be used under controlled conditions in industrial settings. Same reason is valid for use of butyl acrylate as such or in a mixture in consumer products.

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

The described use scenarios for butyl acrylate result in exposure of industrial workers. Five overall exposure scenarios, each with several contributing scenarios are indicated in the registration(s). Some of the calculated Risk Characterization Ratios (RCRs) for the long-term inhalation local effects are close to, but below 1.

In the provided scenarios use of gloves and local exhaust ventilation or respiratory protection has been recommended. Risk characterization for systemic effects have not been performed as the substance is considered not exert long-term systemic toxicity, at doses below local irritation effects on the upper respiratory tract. The evaluating MSCA agrees that the available information supports that the local DNEL for inhalation can be considered protective also for systemic toxicity.

7.14. References

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7.15. Abbreviations

CAS	Chemical abstracts service
CCH	Compliance check
CLH	Harmonized classification
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR	Carcinogenic, Mutagenic or Reprotoxic
CoRAP	Community Rolling Action Plan
CSR	Chemical safety report
DNEL	Derived no effect level
ECHA	European Chemicals Agency
eMSCA	Evaluating Member State Competent Authority
EOGRTS	Extended one-generation reproductive toxicity study
HPRT	Hypoxanthine-guanine Phosphoribosyltransferase
GD	Gestational day
IARC	International agency for research on cancer
IUCLID	International Uniform Chemical Information Database
LD50	Median lethal dose. The dose causing 50 % lethality
MSC	Member State Committee
MSCA	Member State Competent Authority
NCE	Normochromatic erythrocytes
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative, Toxic
PROC	Process category
QSAR	Quantitative structure–activity relationship
RAC	Risk Assessment Committee
STOT SE	Specific target organ toxicity after single exposure
SVHC	Substance of very high concern