# REACH Program

# Justification

# For

# Acrylate category

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# JUSTIFICATION FOR ACRYLATE CATEGORY

# Executive Summary

Data on physico-chemical properties, environmental fate, ecotoxicity, and human health effects have been collected for the following substances: acrylic acid (CAS No. 79-10-7), methyl acrylate (CAS No. 96-33-3), ethyl acrylate (CAS No. 140-88-5), n-butyl acrylate (CAS No. 141-32-2), isobutyl acrylate (CAS No. 106-63-8), tert-butyl acrylate (CAS No. 1663-39-4), and 2-ethylhexyl acrylate (CAS No. 103-11-7). Because these substances exhibit similarity in their physico-chemical properties and toxicological properties in mammals, and because the acrylate esters have been shown to be metabolized in the mammalian body in minutes to acrylic acid and the corresponding alcohol, they can be considered to constitute a chemical category. Data gaps for mammalian toxicity can be addressed by read-across between category members. In addition, because these substances exhibit similarity in their environmental fate and eco-toxicological properties, data gaps in environmental fate and ecotoxicity can be addressed by read-across between category members.

# Chemical Category: Acrylic Acid and Esters

## *1. Identification of category and Rationale for Use*

The Acrylic Acid and Esters category is defined as a structurally related group of substances including acrylic acid (CAS No. 79-10-7), methyl acrylate (CAS No. 96-33-3), ethyl acrylate (CAS No. 140-88-5), n-butyl acrylate (CAS No. 141-32-2), isobutyl acrylate (CAS No. 106-63-8), tert-butyl acrylate (CAS No. 1663-39-4), and 2-ethylhexyl acrylate (CAS No. 103-11-7). All of these chemicals have a common Structure-Activity-Relationship (SAR) to serve as the technical basis for the category.

Article 13(1) of legislation EC1907/2006 (REACH) states that "Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, *in vitro* methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across)."

In the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals, a chemical category is defined as "a group of chemicals whose physico-chemical and human health and/or environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristic)." The guidance then provides a list of characteristic properties upon which structural similarity may be based.

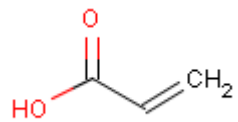
The Acrylates Category proposed herein complies with the REACH definition of an acceptable category based on all criteria cited below, namely

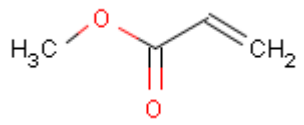
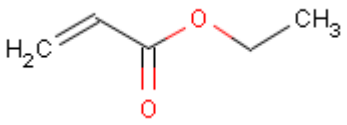
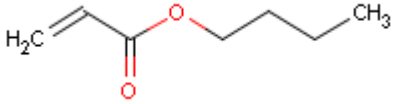
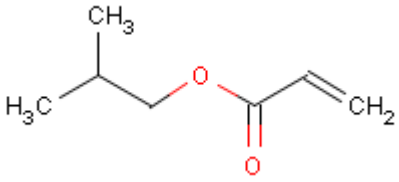
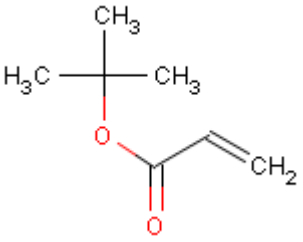
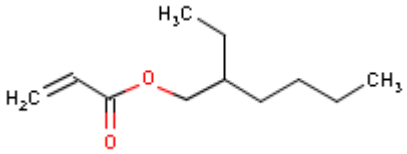
[1] Structural similarities:
- sharing of a common functional group (all are esters of acrylic acid);
- common chemical class, and
- an incremental change in chain length across the category

[2] common breakdown products for related acids and esters.
[3] similarities in physico-chemical, human health, environmental toxicological properties and environmental fate properties

The group consists of molecules based on acrylic acid, and includes esters of the acid of increasing carbon chain length. An overview of the chemicals included in this category are:

**Table 1**: Chemicals included in the Acrylate Category

| | | |
|---|---|---|
|  | | |
| Acrylic acid | | |
| CAS No. 79-10-7 | | |
| Annex X substance | | |

| | | |
|---|---|---|
|  |  |  |
| Methyl acrylate | Ethyl acrylate | n-Butyl acrylate |
| CAS No. 96-33-3 | CAS No. 140-88-5 | CAS No. 141-32-2 |
| Annex X substance | Annex X substance | Annex X substance |
|  |  |  |
| Isobutyl acrylate | tert-Butyl acrylate | 2-Ethylhexyl acrylate |
| CAS No. 106-63-8 | CAS No. 1663-39-4 | CAS No. 103-11-7 |
| Annex IX substance | Tonnage band confidential | Annex X substance |

In the absence of measured data, toxicity of category members can be estimated based on toxicity data derived from tests with acrylic acid and, to a lesser extent, the alcohols associated with the esters. Acrylic acid is produced at a one-to-one molar ratio from each of the esters, as are the associated alcohols.

# *2. Category approach justification*

## 2.1 Structural similarities

The seven members of the group (Table 1) consist of a common backbone: acrylic acid, and an ester of increasing carbon chain length (methyl, ethyl, butyl, isobutyl, tert-butyl, and 2-ethylhexyl).

## 2.2 Similarities in metabolism

With regard to acrylate ester metabolism in mammals, studies have been conducted in order to evaluate the possibility that acrylate esters are hydrolysed to acrylic acid and an alcohol *in vivo* and *in vitro*, and to determine the extent to which acrylic acid and the acrylate esters bind glutathione (GSH) *in vitro* (Miller et al., 1979). The acrylate esters were found to disappear rapidly in rat whole blood *in vitro*; the $t_{½}$ was 3.6, 4.6, and 7.1 minutes for disappearance of methyl, ethyl, and butyl acrylate, respectively.

Subsequent studies demonstrated that acrylic acid was quite stable in rat blood as well as in rat liver, kidney and lung homogenates *in vitro*. Ethyl acrylate disappeared in tissue homogenates *in vitro*; the rate of hydrolysis was ~20 times greater in liver homogenates than in kidney or lung homogenates. Similar results were obtained for methyl acrylate.

Recent investigations on the *in vitro* metabolism of acrylates and methacrylates showed a fast esterase cleavage within the first 10 incubation minutes, with a parallel increase of acrylic acid after incubation with S9 fraction of rat liver for methyl-, ethyl-, n-butyl-, isobutyl, and 2-ethylhexyl acrylate (BASF SE, 2014). The $t_{½}$ was 0.84 min for butyl acrylate, 1.4 min for ethyl acrylate and about 3 min (due to a technical error determined on the acrylic acid formation) for methyl acrylate. In plasma the disappearance was by factor or 10 slower. The rate of hydrolysis of the acrylates in rat liver homogenates increased in the order butyl > ethyl > methyl.

***Selected in vivo study results demonstrating comparable metabolism in mammals:***

***Acrylic acid (CAS No. 79-10-7):*** *C3H mice and Fischer 344 rats, respectively, were treated by gavage (40 or 150 mg/kg bw) with [1-$^{14}$C]-acrylic acid. Mice rapidly absorbed and metabolised orally administered acrylic acid (AA), with about 80% of the dose exhaled as $^{14}CO_2$ within 24 h. Excretion in urine and faeces accounted for approximately 3% and 1% of the dose, respectively. Elimination of the $^{14}$C radiolabel from plasma, liver and kidney was rapid but it was slower from fat. The disposition of orally administered acrylic acid in rats was similar to the results obtained from mice. High-performance liquid chromatography (HPLC) analysis of rat urine and rat and mouse tissues indicated that absorbed AA was rapidly metabolized by the ß-oxidation pathway of propionate catabolism. No unchanged AA was detected 1 h after oral administration; however, several metabolites that were more polar than AA were measured, including 3-hydroxypropionate. Neither AA nor its metabolites were detected at later times after oral administration (Black et al., 1995).*

***Methyl acrylate (CAS No. 96-33-3):*** *Methyl acrylate is rapidly absorbed by the oral and inhalation routes and distributed throughout the body. After oral or intraperitoneal administration, greater than 90 % is excreted within 72 hours, primarily via the lungs as $CO_2$ (> 50 %), and kidneys as products of glutathione conjugation reactions (10-50 %) (Delbressine 1981, Sapota 1988 & 1990, Seutter 1981). The predominant pathway of metabolism of methyl acrylate, by many tissues (including lung, liver, kidney and plasma) appears to be hydrolysis to* ***acrylic acid*** *and* ***methanol****, which is catalyzed by carboxyl esterase enzymes. Thus, under normal circumstances, a relatively small amount of the intact ester is absorbed into the blood through the lungs. The subsequent metabolism will follow that for acrylic acid, and involves*

*metabolism to $CO_2$ via the propionate degradation pathway (**acrylic acid → 3-hydroxypropionic acid → malonyl semialdehyde → acetyl S CoA → tricarboxylic acid cycle → $CO_2$**). Metabolism of methanol proceeds via a catalase peroxidative pathway or alcohol dehydrogenase pathway. Intact methyl acrylate, which reaches the blood, is detoxified by hydrolysis, as well as by conjugation (by Michael addition) with glutathione (GSH) to form thioethers. The conjugates are then converted to mercapturic acids and excreted in the urine. The main conjugate has been identified as N-acetyl-S-(2-carboxyethyl)cysteine. Inhibition of the hydrolytic pathway with carboxylase inhibitor results in increased metabolism via the GSH conjugation route (Silver & Murphy 1981, Miller 1981).*

***Ethyl acrylate (CAS No. 140-88-5):** Toxicokinetic and metabolic studies on rats show that ethyl acrylate is rapidly absorbed after oral and inhalative uptake. The substance is rapidly hydrolyzed to **acrylic acid** and **ethanol** by unspecific carboxylesterases which e.g. were detected in the liver, kidney, lung, plasma, nasal mucous membrane and stomach (Silver & Murphy, 1981; Stott & McKenna, 1984; 1985; De Bethizy et al., 1987; Ghanayem et al., 1987; Vodicka et al., 1990). The half-life of ethyl acrylate in rat blood is less than 15 minutes (Miller et al., 1981). After further metabolism, the substance is mostly exhaled as $CO_2$ (about 70% of the applied dosage within 24 h) or is eliminated with the urine as 3-hydroxypropionic acid (DeBethizy et al., 1987; Ghanayem et al., 1987). After uptake, ethyl acrylate is moreover conjugated in small amounts with non-proteinbound sulfhydryl groups (glutathione) and, following further reaction, is excreted with the urine and faeces in the form of mercapturic acid derivatives (De Bethizy et al., 1987)*

***Butyl acrylate (CAS No. 141-32-2):** After oral administration by gavage, Butyl [2,3-$^{14}$C]-acrylate was rapidly absorbed and metabolized in male Fischer 344 rats, 75 % of the initial dose was eliminated as $CO_2$, approximately 10 % via urine and 2 % via faeces). The major portion of n-butyl acrylate (BA) was hydrolysed by carboxy esterase to **acrylic acid** and **butanol** and then eliminated as $CO_2$. A smaller portion was conjugated with endogenous GSH to be subsequently excreted as mercapturic acids in the urine (Sanders, 1988). After i. v. administration, the labelled BA was rapidly absorbed and metabolized. The acrylate moiety was metabolized primarily to **$CO_2$**, accounting for elimination of up to 45 % of the administered radiolabel. The second major route of elimination was in urine, with only trace amounts in faeces and as volatiles (Sanders, 1988). No parent compound was detected in any of the urine, bile, or tissue extract samples by HPLC analysis. The two major metabolites in urine after both oral and intravenous routes of exposure were identified as **N-acetyl-S-(2-carboxyethyl)cysteine** and **N-acetyl-S-(2-carboxyethyl)cysteine-S-oxide** (Sanders, 1988). Thus, after oral and i. v. administration, BA is rapidly absorbed and metabolized in male rats. The major portion of BA was hydrolysed by carboxy esterase to **acrylic acid** and **butanol**. The subsequent metabolism follows that for acrylic acid, and involves metabolism to $CO_2$ via the propionate degradation pathway (**acrylic acid → 3-hydroxypropionic acid → malonyl semialdehyde → acetyl S CoA → tricarboxylic acid cycle → $CO_2$**). Metabolism of **butanol** proceeds via the **alcohol** and **aldehyde dehydrogenase** pathway. A smaller portion of the administered BA was conjugated with endogenous GSH to be subsequently excreted as mercapturic acids in the urine.*

The alcohols associated with the esters being formed after hydrolysis are methanol (CAS No. 67-56-1), ethanol (CAS No. 64-17-5), butanol (CAS No. 71-36-3), isobutanol (CAS No. 78-83-1), tert-butanol (CAS No. 75-65-0), and 2-ethylhexanol (CAS No. 104-76-7). Except for 2-ethylhexanol harmonized classifications exist for all alcohols. In addition, ECHA disseminated dossiers are available for all alcohols. None of the harmonized classifications and ECHA disseminated dossiers indicate that the alcohols are sensitising, genotoxic, carcinogenic, or reprotoxic.

In conclusion, the toxicokinetic data shows that the acrylate esters are rapidly absorbed and metabolized. As a result, the toxicity data derived from acrylic acid and the alcohols associated with the esters can be used to facilitate read-across to fill the few remaining data gaps and supports individual member study results.

## 2.3 Similarities in physico-chemical, environmental fate, ecotoxicity and human health effects

Review of the data currently available on these compounds confirms the validity of this category, with similar/predictable activity in regard to physico-chemical properties, environmental fate, ecotoxicity and human health effects. All data are summarized in IUCLID dossiers for individual category members. Below a summary has been made based on the available data.

### 2.3.1 Physico-chemical Properties

Most physico-chemical properties for the category members are quite similar. The data on relevant physico-chemical properties are summarised in Table 2 of Annex I.

All substances in the category are liquids. Acrylic acid (CAS No. 79-10-7) has the highest melting point of 13°C while the melting point of the acrylate esters range from -90 to -61°C. Boiling points range from 80.1 to 215°C. 2-Ethylhexyl acrylate (CAS No. 103-11-7) has the lowest vapour pressure of 0.24 hPa and methyl acrylate (CAS No. 96-33-3) the highest of 90 hPa. Water solubility and partition coefficient decreases and increases, respectively, with increasing length of the ester carbon chain. Acrylic acid has the highest water solubility of 1000 g/L and the lowest partition coefficient of 0.46 while 2-ethylhexyl acrylate has the lowest water solubility of 0.01 g/L and the highest partition coefficient of 4.0.

### 2.3.2 Environmental Fate

A summary of the relevant environmental fate properties are given in Table 3 of Annex I. Results from biodegradation studies consistently indicate a high potential for ready biodegradability except for tert-butyl acrylate (CAS No. 1663-39-4) which, due to its branched molecular structure, is moderately biodegradable. Hydrolysis of acrylic acid and the acrylate esters is negligible and does not significantly contribute to the degradation of the substances under environmental conditions. The exception is 2-ethylhexyl acrylate (CAS No. 103-11-7) which will hydrolyse slowly in contact with water. Measured and calculated Koc values indicate that absorption to soil of acrylic acid and the acrylate esters is not to be expected. Calculated bioconcentration factors indicate that 2-ethylhexyl acrylate (BCF = 282) may accumulate in organisms, but as 2-ethylhexyl acrylate will be rapidly hydrolysed in organisms no significant bioaccumulation is to be expected. For acrylic acid and the other acrylate esters accumulation in organisms is not to be expected based on the calculated bioconcentration factors.

### 2.3.3 Ecotoxicity

A summary of the relevant ecotoxicological properties are given in Table 4 of Annex I. For acrylic acid (CAS No. 79-10-7), LC50 value in freshwater fish is 27 mg/L, EC50 of freshwater invertebrates (Daphnia magna) is 47 mg/L, and EC50 values in freshwater algae is 0.13 mg/L. Thus, the algae is by far the most sensitive species for acrylic acid. In the chronic studies an algae EC10 of 0.03 mg/L and an invertebrate NOEC of 12 mg/L has been derived.

For the acrylate esters, LC50 values in freshwater fish ranged from 1.81 and 5.2 mg/L, EC50 values in freshwater invertebrates (Daphnia magna) were between 1.3 and 8.74 mg/L, and EC50 values in freshwater algae were between 1.71 and 14.6 mg/L, respectively. Thus, effect values were all in the same range of concentrations with Daphnia magna as the most sensitive freshwater species by a narrow margin. A 21-day chronic life-cycle study with Daphnia magna is available with ethyl acrylate (CAS No. 140-88-5) with a NOEC of 0.19 mg/L, and another with n-butyl acrylate (CAS No. 141-32-2) with a NOEC of 0.136 mg/L. In addition, several NOEC values from studies in algal species are available ranging from 0.45 to 3.85 mg/L.

As a result, the six acrylic esters (methyl, ethyl, n-butyl, isobutyl, tert-butyl, and 2-ethylhexyl) were evaluated as a category regarding ecotoxicity and the lowest NOEC value available was used in the derivation of the PNECs of aquatic organisms.

## 2.3.4 Human health effects

A summary of the relevant human health properties are given in Table 5 of Annex I.

**Acute Toxicity**

Acrylic acid and the acrylate esters are low to moderately toxic after oral, inhalation and dermal exposure.

**Irritation**

Acrylic acid (CAS No. 79-10-7) is corrosive to skin and eye. All acrylate esters of this category are irritating to skin, but differ in the irritating properties towards the eye. The eye irritancy of the acrylate esters decreases with increasing length of the ester carbon chain.

**Sensitisation**

All acrylates are considered to be sensitizing to skin with EC3 values ranging from 9.7 to 36.8% indicating that acrylates are moderate skin sensitizers. For isobutyl acrylate (CAS No. 106-63-8) and tert-butyl acrylate (CAS No. 1663-39-4) no studies investigating skin sensitization are available, but as other acrylates of this category are sensitizing to skin, isobutyl acrylate and tert-butyl acrylate are also considered to be skin sensitizing. Acrylic acid (CAS No. 79-10-7) is the only substance from the acrylate category which is not a skin sensitizer.

**Repeated Dose Toxicity**

Tests ranging from 28 days to 2 years with acrylate category members demonstrate similar effects in rats and mice via both inhalation and dietary routes of administration. The NOAEL for repeated dose toxicity for the various members of this category is consistent, and within a relatively narrow range (5 to 108 ppm for inhalation, 5 to 84 mg/kg bw for oral exposure), based on an evaluation of all the repeated dose toxicity studies. None of the members tested produced evidence of carcinogenicity in chronic/oncogenicity studies of known relevance to humans. These repeated dose toxicity studies have also reported a similar and common profile of target organs. Thus, the results of the collection of sub-chronic and chronic studies conducted on these substances are consistent and can be regarded as offering a true picture of repeated dose toxicity.

**Genetic Toxicity**

For all substances of the category only negative results were observed in Ames tests.

Acrylic acid (CAS No. 79-10-7) did not induce gene mutations in a HGPRT test but was positive in the mouse lymphoma assay and in the *in vitro* chromosomal aberration test. Since in the mouse lymphoma assay mainly small colonies were formed, the mutagenic potential of acrylic acid seems to be limited to clastogenicity. *In vivo*, acrylic acid did not induce mutagenic effects in either rat bone marrow cells or mouse germ cells after oral administration.

Methyl acrylate (CAS No. 96-33-3) was negative in gene mutation assays in mammalian cells (HGPRT and XPRT assays), but was positive in the mouse lymphoma TK mutation assay in the absence of metabolic activation. However, these positive results were observed at clearly cytotoxic concentrations (≤ 50% cell survival) and the majority of the mutant colonies were small colonies, suggesting that methyl acrylate acts via a clastogenic mechanism *in vitro*. *In vivo*, methyl acrylate was negative in several mouse micronucleus assays.

For ethyl acrylate (CAS No. 140-88-5), *in vitro* identical results were observed compared to methyl acrylate: negative HPRT assay, positive mouse lymphoma TK mutation assay with small mutant colonies and several negative *in vivo* mouse micronucleus assays and chromosome aberration tests. In addition ethyl acrylate was tested in the in vivo gene mutation assay in *gpt* Delta Mice according to OECD TG 488. The mutant frequencies (6-thioguanine and Spi- selection) in the liver and stomach of all groups treated by oral gavage with ethyl acrylate were not increased, therefore ethyl acrylate was negative for genotoxicity in this test system.
n-Butyl acrylate (CAS No. 141-32-2) was negative in an *in vitro* micronucleus assay and in an *in vitro* UDS assay in Syrian hamster embryo fibroblasts. *In vivo*, n-butyl acrylate showed no genotoxic effects after vapour inhalation exposure in rats and hamsters in a chromosome aberration assay.
Isobutyl acrylate (CAS No. 106-63-8) was not clastogenic *in vivo* in a mouse micronucleus test. Tert-butyl acrylate (1663-39-4) was not clastogenic *in vivo* in a mouse micronucleus test and not mutagenic in a HPRT test in V79 cells.
2-Ethylhexyl acrylate (CAS No. 103-11-7) did not induce gene mutations in a HGPRT test but was positive in the mouse lymphoma TK mutation assay. The *in vitro* chromosomal aberration test gave inconclusive results. Inconclusive results were also obtained from the *in vivo* chromosomal aberration assay. The *in vivo* UDS assay was negative.

In conclusion, Ames tests performed with all seven substances indicate that the members of the category are not mutagenic to bacteria. Regarding mutagenicity in mammalian cells, consistently a negative effect in the HPRT assays, but a positive result in the mouse lymphoma TK mutation assays was observed. The positive results were observed at cytotoxic concentrations and the mutant colonies were small indicating a clastogenic mechanism to be responsible for this effect. As in the *in vitro* and *in vivo* micronucleus assays, in the *in vivo* chromosome aberration assays and in the in vivo gene mutation assay in *gpt* Delta mice no genotoxic potential was observed, it can be concluded that all members of the acrylate category are not genotoxic.

**Carcinogenicity**
Tests regarding carcinogenicity are available for acrylic acid and four of the acrylate esters.
Oral carcinogenicity tests have been performed with acrylic acid (CAS No. 79-10-7) showing no evidence of carcinogenicity in a 2-year drinking water study in Wistar rats up to the highest dose tested of 78 mg/kg bw. A chronic drinking water study with ethyl acrylate (CAS No. 140-88-5) in rats did also not result in evidence of carcinogenicity. However, long-term exposure to ethyl acrylate at high concentrations by gavage administration induced marked local irritation and cellular proliferation and led to forestomach tumours in rats and mice. However, forestomach tumours are not considered to be relevant for humans

Methyl acrylate (CAS No. 96-33-3) and n-Butyl acrylate (CAS No. 141-32-2) showed no evidence of carcinogenicity in a 2-year vapour inhalation study in Sprague-Dawley rats up to the highest tested dose (135 ppm) which is equivalent to 0.52 mg/L and 0.78 mg/L, respectively. Ethyl acrylate showed no evidence of carcinogenicity in rats or mice following chronic inhalation to atmospheres of 75 and 225 ppm (corresponding to approx. 0.31 and 0.92 mg/L), respectively.

In two dermal carcinogenicity studies in three mice strains, exposed to acrylic acid, the frequency of skin tumours was not elevated compared to the vehicle controls. In addition, lifetime dermal exposure of mice to ethyl acrylate did not result in a positive tumour response. Furthermore, n-butyl acrylate showed no evidence of carcinogenicity in a lifetime skin painting study in C3H/HeJ mice at approx. 8 mg/kg bw. However, in a dermal mouse (C3H) carcinogenicity study, 2-ethylhexyl acrylate (CAS No. 103-11-7) induced skin tumours at concentrations which were highly irritating. However, at a lower concentration of 2.5%, transient irritation but no tumour response of the skin was observed. Irritative skin damage was

identified as presumed mode of tumourigenicity. In addition, other dermal long-term studies with 2-ethylhexyl acrylate on different mouse strains (NMRI) did not confirm tumour induction of the mouse skin. As there is no concern from tumour data of acrylic acid and 2-ethylhexanol, the cleavage products of 2-ethylhexyl acrylate, and taking into account that skin painting studies in mice have a limited reliability as a tool to identify the carcinogenic potential of a test substance, there are no reasons to assume that 2-ethylhexyl acrylate might have a carcinogenic potential.

**Fertility**

Two members of the category have been tested in classic reproduction studies, in addition results of sub-chronic and chronic tests with all category members indicate no effects on reproductive organs.

Acrylic acid (CAS No. 79-10-7) has been tested in a two-generation reproduction study. The NOAEL for reproductive effects was 460 mg/kg bw (highest dose tested), while the NOAEL for parental toxicity reached a low of 53 mg/kg bw in the F1 generation and 240 mg/kg bw in the P-generation. There was no indication of reproductive effects at any dose level tested. In addition, in a guideline one-generation reproduction study, the NOAEL for reproductive effects was 250 mg/kg bw while parental toxicity was determined to be 83 mg/kg bw.

A two-generation reproduction study has been conducted for methyl acrylate (CAS No. 96-33-3) to provide data to close the data gaps. In this study, the NOEC for parental systemic toxicity was determined to be 0.02 mg/L (5 ppm) and was based on histologic changes in the nasal tissues seen at higher concentrations. The NOEC for developmental toxicity was 0.09 mg/L (25 ppm), based on decreases in pup body weight at 75 ppm which were secondary to parental toxicity. The NOEC for reproductive toxicity was 0.27 mg/L (75 ppm), the highest concentration tested.

As the acrylate esters are metabolized to acrylic acid and its associated alcohol, and none of the alcohols are classified for reproduction toxicity, it can be concluded that acrylic acid and the six acrylate esters do not affect fertility.

**Developmental Toxicity**

Developmental toxicity studies in rats, performed in accordance with or similar to OECD 414, are available for acrylic acid, and all acrylate esters except for isobutyl acrylate (CAS No. 106-63-8) and tert-butyl acrylate (CAS No. 1663-36-4) which was tested in a combined OECD 413/422 study. In none of these studies developmental effects are observed in the absence of maternal toxicity.

For acrylic acid (CAS No. 79-10-7) and methyl acrylate (CAS No. 96-33-3) developmental toxicity studies, performed in accordance with OECD 414, in rabbits are available. In both studies no developmental effects are observed in the absence of maternal toxicity.

The overall weight of evidence based on the data on acrylic acid and several acrylate esters gives no indications that the members of this class of chemicals are developmental toxicants. Only in overt maternal toxic concentrations developmental effects, probably as secondary effect were described for this class of acrylates.

# 3 Conclusion for C&L per endpoint

The classification and labelling of the substances of the acrylate category are given in Table 6 of Annex I.

Evaluation of the chemicals in this category leads to the conclusions that [1] data currently exist to adequately represent the toxicological and ecological profile of major portions of this category, [2] there is a concurrence and similarity among the existing data for the various endpoints and [3] toxicokinetic data shows that all acrylate esters are rapidly absorbed and metabolized to acrylic acid and their associated alcohol. As a result, the toxicity data derived from acrylic acid and the alcohols associated with the esters can be read-across to fill the few remaining data gaps and can support individual category member study results.

No data gaps exist for acrylic acid (CAS No. 79-10-7) and subsequently no read-across has to be performed for this substance.

For isobutyl acrylate (CAS No. 106-63-8) data is missing for acute and chronic toxicity to aquatic invertebrates, for methyl acrylate (CAS No. 96-33-3), tert-butyl acrylate (CAS No. 1663-39-4) and 2-ethylhexyl acrylate (CAS No. 103-11-7) data is missing for chronic toxicity to aquatic invertebrates.
As for all other members of this category a full dataset for the three trophic levels is available, the most sensitive freshwater organism for the acrylic esters was Daphnia magna (EC50 = 1.3 mg/L), and as a worst-case approach the lowest NOEC (from a chronic daphnia study) value was used in the derivation of the PNECs of aquatic organisms, it can be concluded that no additional testing is required.

For isobutyl acrylate (CAS No. 106-63-8) data is missing for repeated dose toxicity and *in vitro* mutagenicity to mammalian cells.
Regarding repeated dose toxicity studies, the NOAEL for repeated dose toxicity for the various members of this category is consistent. In addition, as isobutyl acrylate is metabolized rapidly to acrylic acid and isobutanol, and acrylic acid and isobutanol is not classified for repeated dose toxicity (STOT RE), it can be concluded that acrylic acid no additional repeated dose toxicity data is required, and thus no further testing is needed.
Regarding genetic toxicity, no information on *in vitro* mutagenicity to mammalian cells is available. Based on other tests performed with this substance, isobutyl acrylate is not mutagenic to bacteria and is not clastogenic *in vivo*. Similar results were obtained for the other members of the category. These other category members consistently showed a negative effect in the HPRT assays, but a positive result in the mouse lymphoma TK mutation assays. However, as these positive results were caused via a clastogenic mechanism and an *in vivo* mouse micronucleus test with isobutyl acrylate was negative, it can be concluded that isobutyl acrylate, like its category members, is not genotoxic and no additional tests have to be performed.

For isobutyl acrylate and tert-butyl acrylate (CAS No. 1663-39-4) data is missing regarding the skin sensitising properties of both substances. As all acrylate esters are considered to be sensitizing to skin, isobutyl acrylate and tert-butyl acrylate are also considered to be skin sensitizing. Therefore, no additional testing investigating skin sensitising properties is required.

For none of the acrylate esters, except methyl acrylate, an extended one-generation reproductive toxicity study or a two-generation reproduction toxicity study are available. For ethyl acrylate (CAS No. 140-88-5), n-butyl acrylate (CAS No. 141-32-2), and 2-ethylhexyl acrylate (CAS No. 103-11-7) no effects on the

reproductive organs were observed in repeated dose toxicity tests. Acrylic acid has been tested in a two-generation reproduction toxicity study and in an one-generation reproduction toxicity study and methyl acrylate has been tested in a two-generation reproduction toxicity study. In these studies, no indication of reproductive effects were observed in the absence of parental toxicity. As the acrylate esters are metabolized rapidly to acrylic acid and its respective alcohol, and none of the alcohols are classified for reproduction toxicity, it can be concluded that acrylic acid and the six acrylate esters do not affect fertility in the presence of parental toxicity. Subsequently, no additional reproduction toxicity data is required.

Developmental toxicity studies in rats, performed in accordance with or similar to OECD 414, are available for acrylic acid, and all acrylate esters except for isobutyl acrylate (CAS No. 106-63-8) and tert-butyl acrylate (CAS No. 1663-36-4) which was tested in a combined OECD 413/422 study. Furthermore, for the acrylate esters except methyl acrylate no developmental toxicity data in rabbits is available. The overall weight of evidence based on the data on acrylic acid and several acrylate esters gives no indications that the members of this class of chemicals are developmental toxicants as only in overt maternal toxic concentrations developmental effects were described. As the acrylate esters are metabolized rapidly to acrylic acid and its respective alcohol, and none of the alcohols are classified for developmental toxicity, it can be concluded that acrylic acid and the six acrylate esters are not developmental toxicants. Subsequently, no additional developmental toxicity data is required.

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# Annex 1

**Table 2:** Physico-chemical properties

| | 79-10-7 | 96-33-3 | 140-88-5 | 141-32-2 | 106-63-8 | 1663-39-4 | 103-11-7 |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Molecular weight** | 72.1 | 86.1 | 100.1 | 128.2 | 128.2 | 128.2 | 184.3 |
| **Physical form** | Liquid | Liquid | Liquid | Liquid | Liquid | Liquid | Liquid |
| **Melting Point (°C)** | 13 | -76.5 | -71.2 | -64.6 | -61 | -69 | -90 |
| **Boiling Point (°C)** | 141 | 80.1 | 99.8 | 147 | 132 | 119.2 | 215 |
| **Vapour Pressure (hPa at 25°C)** | 5.29 | 90 (20°C) | 40 (21°C) | 5 (22°C) | 10 | 20 (23°C) | 0.24 |
| **Water Solubility (g/L at 25°C)** | 1000 | 60 | 20 (20°C) | 1.7 (20°C) | 1.8 | 2 (20°C) | 0.01 |
| **Partition Coefficient (at 25°C)** | 0.46 | 0.74 | 1.18 | 2.38 | 2.38 | 2.32 | 4.0 |

**Table 3:** Environmental fate properties

| | 79-10-7 | 96-33-3 | 140-88-5 | 141-32-2 | 106-63-8 | 1663-39-4 | 103-11-7 |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Hydrolysis (DT50)** | No hydrolysis at pH 3, 7, and 11 | 1.8 hours at pH 11:<br>No significant hydrolysis at pH 3 and 7 | 6700 days at pH 3<br>1500 days at pH 7<br>182 min at pH 11 | 2800 days at pH 3<br>1100 days at pH 7<br>243 min at pH 11 | 16.5 years at pH 7<br>1.6 years at pH 8<br>(QSAR) | 23.6 years at pH 7<br>2.4 years at pH 8<br>(QSAR) | 533 hours at pH 3<br>210 hours at pH 7<br>18.5 hours at pH 11 |
| **Biodegadation** | Readily biodegradable | Readily biodegradable | Readily biodegradable | Readily biodegradable | Readily biodegradable | Partly or moderately biodegradable | Readily biodegradable |
| **Bioaccumulation (BCF)** | 3.16 (QSAR) | 3.16 (QSAR) | 2.0 (QSAR) | 17.3 (QSAR) | 17.3 (QSAR) | 15.8 (QSAR) | 282 (QSAR) |
| **Adsorption/Desorption (Measured Koc)** | 42.8 | - | 42.2 | 88.4 | - | - | - |
| **Adsorption/Desorption (Calculated Koc)** | 1.2 | 6.4 | 11.9 | 35.4 | 33.8 | 26.1 | 429 |

**Table 4:** Ecotoxicological properties

| | **79-10-7** | **96-33-3** | **140-88-5** | **141-32-2** | **106-63-8** | **1663-39-4** | **103-11-7** |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Acute Fish (LC50) (Fresh water)** | 27 mg/L | 3.4 mg/L | 4.6 mg/L | 5.2 mg/L | 2.1 mg/L | 2.37 mg/L | 1.81 mg/L |
| **Acute Fish (LC50) (Marine water)** | 236 mg/L | 1.1 mg/L | 2.0 mg/L | 2.1 mg/L | **RA (n-Butyl acrylate)** | **RA (n-Butyl acrylate)** | - |
| **Acute Invertebrates (EC50)** | 47 mg/L (fresh water)<br>97 mg/L (LC50) (marine water) | 2.6 mg/L (fresh water)<br>1.6 mg/L (marine water) | 7.9 mg/L (fresh water) | 8.2 mg/L (fresh water) | **RA (n-Butyl acrylate)** | 8.74 mg/L (fresh water) | 1.3 mg/L |
| **Chronic Invertebrates** | 12 mg/L (NOEC) | **RA (n-Butyl acrylate and Ethyl acrylate)** | 0.19 mg/L (NOEC) | 0.136 mg/L (NOEC) | **RA (n-Butyl acrylate and Ethyl acrylate)** | **RA (n-Butyl acrylate and Ethyl acrylate)** | **RA (n-Butyl acrylate and Ethyl acrylate)** |
| **Algae (ErC50)** | 0.13 mg/L | 3.55 mg/L | 4.5 mg/L (Cell number) | 2.65 mg/L (Cell number) | 5.28 mg/L | 14.6 mg/L | 1.71 mg/L |
| **Algae (ErC10)** | 0.03 mg/L | - | - | - | 0.82 mg/L (NOEC) | 3.85 mg/L (NOEC) | 0.45 mg/L (NOEC) |
| **Micro-organisms** | EC20 (30 min) 900 mg/L | EC10 (3d) > 100 mg/L | EC10 (72h) > 100 mg/L | EC0 (3d) > 150 mg/L | EC20 (30 min) > 1000 mg/L | EC20 = ca. 950 mg/L | EC20 (30 min) > 1000 mg/L |

**Table 5:** Human health properties

| | **79-10-7** | **96-33-3** | **140-88-5** | **141-32-2** | **106-63-8** | **1663-39-4** | **103-11-7** |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Acute oral (LD50: mg/kg bw)** | >1000<2000 (rat) | 768 (rat) | 1120 (rat) | 3150 (rat) | 4895 (rat) | 1047 (rat) | 4435 (rat) |

| | **79-10-7** | **96-33-3** | **140-88-5** | **141-32-2** | **106-63-8** | **1663-39-4** | **103-11-7** |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Acute inhalation (LD50: mg/L)** | > 5.1 (rat) | 10.4 (rat) | 9.1 (rat) | 10.3 (rat) | 10.5 (rat) | 7.01 (rat) | - |
| **Acute dermal (LD50: mg/kg bw)** | >2000 (rabbit) | 1250 (rabbit) | 3049 (rat) | 2000 (rabbit) | 793 (rabbit) | 2000 (rabbit) | 7522 (rabbit) |
| **Skin irritation** | Corrosive | Irritating | Irritating | Irritating | Irritating | Irritating | Irritating |
| **Eye irritation** | Corrosive | Serious eye damage | Irritating | Irritating | Not irritating | Not irritating | Not irritating |
| **Skin sensitisation** | Not sensitising | Sensitising EC3 = 19.6% | Sensitsing EC3 = 36.8% | Sensitising EC3 = 11.2% | **RA (n-Butyl acrylate)** | **RA (n-Butyl acrylate)** | Sensitising EC3 = 9.7% |
| **Repeated dose toxicity (oral NOAEL)** | 83 mg/kg bw (similar to OECD 408, rat)<br><br>40 mg/kg bw (similar to OECD 452, rat) | 5 mg/kg bw (similar to OECD 408, rat) | <20 mg/kg bw (similar to OECD 408, rat)<br><br>55 mg/kg bw (similar to OECD 408, rat) | 84 mg/kg bw (similar to OECD 408, rat) | **RA (n-Butyl acrylate)** | - | - |

| | **79-10-7** | **96-33-3** | **140-88-5** | **141-32-2** | **106-63-8** | **1663-39-4** | **103-11-7** |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Repeated dose toxicity (inhalation NOAEL)** | Systemic: >0.22 mg/L (>75 ppm) Local: 0.07 mg/L (25 ppm) (similar to OECD 413, rat)<br><br>Systemic: 0.015 mg/L (5 ppm) Local: <0.015 mg/L (<5 ppm) (similar to OECD 413, mice) | Systemic and local: 0.08 mg/L (23 ppm) (similar to OECD 413, rat) | Systemic: 0.10 mg/L (25 ppm) Local: 0.02 mg/L (5 ppm) (similar to OECD 413 and 453, rat and mice) | Systemic: 0.57 mg/L (108 ppm) Local: 0.11 mg/L (21 ppm) (similar to OECD 413, rat) | **RA (n-Butyl acrylate)** | Systemic and local: 0.32 mg/L (60 ppm) (OECD 413/422 study, rat) | Systemic: 0.23 mg/L (30 ppm) Local: 0.075 mg/L (10 ppm) (OECD 413, rat) |
| **Genetic toxicity** | | | | | | | |
| **- Ames test** | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| **- In vitro clastogenicity** | CA: Positive | CA: Positive at >60% cytotoxicity | CA: Positive | MN: Negative CA: Negative SCE: Positive | - | - | MN: Negative CA: Inconclusive |
| **- In vitro mutagenicity** | TK: Positive HPRT: Negative | TK: Positive HPRT: Negative | TK: Positive HPRT: Negative | UDS: Negative<br><br>***Test proposal (OECD TG 490)*** | **RA (Methyl acrylate and Ethyl acrylate)** | HPRT: Negative | TK: Positive HPRT: Negative |
| **- In vivo genotoxicity** | CA: Negative DLA: Negative | MN: Negative | CA: Negative MN: Negative OECD TG 488 (gpt Delta mouse): Negative | CA: Negative | MN: Negative | MN: Negative | CA: Inconclusive UDS: Negative |

| | 79-10-7 | 96-33-3 | 140-88-5 | 141-32-2 | 106-63-8 | 1663-39-4 | 103-11-7 |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Carcinogenicity** | Negative (Rat, oral)<br>Negative (Mice, dermal) | Negative (Rat, inhalation) | Negative (Rat, oral)<br>Negative (Rat, inhalation)<br>Negative (Mice, dermal) | Negative (Rat, inhalation)<br>Negative (Mice, dermal) | **RA (n-Butyl acrylate)** | **RA (n-Butyl acrylate)** | Negative (Mice, dermal) |
| **Fertility** | P (general): 240 mg/kg bw<br>F1 (general): 53 mg/kg bw<br>F2 (general): 53 mg/kg bw<br>P/F1 (fertility): 460 mg/kg bw (oral, OECD 416)<br><br>P (general): 83 mg/kg bw<br>P (fertility): 250 mg/kg bw<br>F1 (general): 250 mg/kg bw (oral, OECD 415) | Parental: 0.02 mg/L (5 ppm)<br>Fertility: >0.27 mg/L (75 ppm)<br>Developmental: 0.09 mg/L (25 ppm) (inhalation, OECD 416) | No effects reproduction organs in repeated dose toxicity studies<br><br>**RA (Methyl acrylate)** | No effects reproduction organs (Inhalation, similar to OECD 413)<br><br>**RA (Methyl acrylate)**<br><br>***Study proposal (OECD TG 414, rabbits)*** | **RA (Methyl acrylate)** | Parental: 0.32 mg/L (60 ppm)<br>Fertility: 0.32 mg/L (60 ppm) (inhalation, OECD 413/422 study)<br><br>**RA (Methyl acrylate, n-Butyl acrylate, and 2-Ethylhexyl acrylate)** | No effects reproduction organs (Inhalation, OECD 413)<br><br>**RA (Methyl acrylate)** |

| | 79-10-7 | 96-33-3 | 140-88-5 | 141-32-2 | 106-63-8 | 1663-39-4 | 103-11-7 |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Developmental (rat) NOAEC/NOAEL** | Maternal: 0.12 mg/L Developmental: 1.1 mg/L (inhalation, OECD 414) | Maternal: 0.09 mg/L (25 ppm) Developmental: 0.18 mg/L (50 ppm) (inhalation, similar to OECD 414) | Maternal: 0.41 mg/L (100 ppm) Developmental: >0.82 mg/L (200 ppm) (inhalation, similar to OECD 414)<br><br>Maternal: 0.21 mg/L (50 ppm) Developmental: >0.62 mg/L (150 ppm) (inhalation, similar to OECD 414) | Maternal: 100 mg/kg bw Developmental: 1000 mg/kg bw (oral, mice, similar to OECD 414)<br><br>Maternal: 0.13 mg/L (25 ppm) Developmental: 0.13 mg/L (25 ppm) (inhalation, similar to OECD 414)<br><br>Maternal: <0.52 mg/L (<100 ppm) Developmental: 0.52 mg/L (100 ppm) (inhalation, similar to OECD 414) | **RA (n-Butyl acrylate)** | Maternal: 0.32 mg/L (60 ppm) Developmental: 0.32 mg/L (60 ppm) (inhalation, OECD 413/422 study)<br><br>**RA (Methyl acrylate, Ethyl acrylate, n-Butyl acrylate, and 2-Ethylhexyl acrylate)** | Maternal: 0.56 mg/L (75 ppm) Developmental: 0.75 mg/L (100 ppm) (inhalation, similar to OECD 414) |
| **Developmental (rabbit) NOAEC/NOAEL** | Maternal: 0.075 mg/L Developmental: 0.673 mg/L (inhalation, OECD 414) | Maternal: 0.06 mg/L (15 ppm) Developmental: >0.16 mg/L (45 ppm) (inhalation, OECD 414) | **RA (Methyl acrylate)** | **RA (Methyl acrylate)**<br><br>***Study proposal (OECD TG 443*)** | **RA (Methyl acrylate)** | **RA (Methyl acrylate)** | **RA (Methyl acrylate)** |

CA = Chromosome aberration; HPRT = In Vitro Mammalian Cell Gene Mutation Tests using the Hprt gene; DLA = Dominant Lethal Assay, MN = Micronucleus; RA = Read-across, TK = In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene, UDS = Unscheduled DNA Synthesis

**Table 6**: Classification and labelling

| | **79-10-7** | **96-33-3** | **140-88-5** | **141-32-2** | **106-63-8** | **1663-39-4** | **103-11-7** |
|---|---|---|---|---|---|---|---|
| | **Acrylic acid** | **Methyl acrylate** | **Ethyl acrylate** | **n-Butyl acrylate** | **Isobutyl acrylate** | **tert-Butyl acrylate** | **2-Ethylhexyl acrylate** |
| **Flammability** | Flam. Liquid 3 | Flam. Liquid 2 | Flam. Liquid 2 | Flam. Liquid 3 | Flam. Liquid 3 | Flam. Liquid 2 | - |
| **Acute oral toxicity** | Acute Tox. 4 | Acute Tox. 4 | Acute Tox. 4 | - | - | Acute Tox. 4 | - |
| **Acute dermal toxicity** | - | Acute Tox. 4 | Acute Tox. 4 | - | Acute Tox. 4 | Acute Tox. 4 | - |
| **Acute inhalation toxicity** | Acute Tox. 4 | Acute Tox. 3 | Acute Tox. 3 | Acute Tox. 4 | Acute Tox. 4 | Acute Tox. 3 | - |
| **Skin corrosion/irritation** | Skin Corr. 1A | Skin Irrit. 2 | Skin Irrit. 2 | Skin Irrit. 2 | Skin Irrit. 2 | Skin Irrit. 2 | Skin Irrit. 2 |
| **Serious eye damage/irritation** | - | Eye Irrit. 2 | Eye Irrit. 2 | Eye Irrit. 2 | - | - | - |
| **Sensitising** | - | Skin Sens. 1B | Skin Sens. 1B | Skin Sens. 1B | Skin Sens. 1B | Skin Sens. 1B | Skin Sens. 1B |
| **Specific target organ toxicity - single** | STOT Single Exp. 3 | STOT Single Exp. 3 | STOT Single Exp. 3 | STOT Single Exp. 3 | STOT Single Exp. 3 | STOT Single Exp. 3 | STOT Single Exp. 3 |
| **Short-term aquatic** | Aquatic Acute 1 | - | - | - | - | - | - |
| **Long-term aquatic** | Aquatic Chronic 2 | Aquatic Chronic 3 | Aquatic Chronic 3 | Aquatic Chronic 3 | Aquatic Chronic 3 | Aquatic Chronic 2 | Aquatic Chronic 3 |