Regulatory Toxicology and Pharmacology 143 (2023) 105469

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Cancer weight of evidence for three lower acrylates: Conclusions and recommendations from an expert panel

C.R. Kirman [a,*], P.J. Boogaard [b], J.S. Bus [c], V.L. Dellarco [d], L.R. DePass [e], B.R. Stern [f], S.M. Hays [a]

[a] SciPinion LLC, Bozeman, MT, 59715, USA
[b] Wageningen University & Research, Wageningen, NL, USA
[c] Exponent, Midland, MI, USA
[d] Independent Consultant, Silver Spring, MD, USA
[e] Durect Corp, Cupertino, CA, 95014, USA
[f] Independent Consultant, San Francisco, CA, USA

ARTICLE INFO

Handling Editor: Dr. Martin Van den berg

Keywords:
Expert panel
Weight of evidence
Mode of action
Genotoxicity
Carcinogenicity
Risk assessment

ABSTRACT

An international panel of experts was engaged to assess the cancer weight of evidence (WOE) for three lower acrylates: methyl acrylate, ethyl acrylate, and 2-ethylhexyl acrylate. The review was structured as a three-round, modified Delphi format, a systematic process for collecting independent and deliberative input from panel members, and it included procedural elements to reduce bias and groupthink. Based upon the available science, the panel concluded: (1) The MOA for point of contact tumors observed in rodent cancer bioassays that is best supported by available data involves increased cell replication by cytotoxicity and regenerative proliferation; (2) The WOE supports a cancer classification of "Not likely to be carcinogenic to humans" a conclusion that is more in line with an IARC classification of Group 3 rather than Group 2 B; (3) Quantitative cancer potency values based on rodent tumor data are not required for these chemicals; and (4) Human health risk assessment for these chemicals should instead rely on non-cancer, precursor endpoints observed at the point of contact (e.g., hyperplasia). The degree of consensus (consensus scores of 0.84–0.91 out of a maximum score of 1) and degree of confidence (7.7–8.7 out of a maximum score of 10) in the WOE conclusions is considered high.

1. Introduction

Acrylates are esters of acrylic acid with carbon chains of varying length. As a group, acrylates are important industrial chemicals used in the synthesis of polymers that in turn are used in a variety of consumer products, including adhesives, cosmetics, paints and coatings, plastics, synthetic flavors, and textiles (IARC, 2019). Human populations can be exposed to acrylates by multiple pathways. These exposures are primarily via inhalation and dermal contact, while ingestion is generally considered negligible, and include occupational exposures and through use of consumer products that contain them. Occupational exposures to acrylates are generally low (<5 ppm), although peak measurements that exceed 10 ppm have been reported for specific tasks, which were accompanied by use of personal protective equipment by workers (Suh et al., 2018). Trace levels of some acrylates (e.g., ethyl acrylate<20 ppm; 2-ethylhexylacrylate<100–1000 ppm) have been detected in copolymers used for cosmetics. The potential for environmental exposures to these acrylates via air, water and soil are generally considered low. Natural sources of methyl and ethyl acrylates include certain fruits (e.g., pineapples) (Suh et al., 2018). Acrylates have strong odors with low odor thresholds thereby limiting occupational exposures (Suh et al., 2018), and as reactive chemicals produce irritation and toxicity at the point of contact (Brüning et al., 2014). Once absorbed, acrylates are rapidly metabolized through two pathways: (1) hydrolysis via carboxylesterase to form acrylic acid and an alcohol corresponding to the carbon side chain; and (2) conjugation with glutathione (Suh et al., 2018; IARC, 2019). Metabolism of acrylates is considered to be detoxifying, and due to its rapid nature (several minutes), systemic doses of acrylates are generally expected to be much lower than those experienced at the point of contact.

This assessment was defined to consider the cancer weight of evidence and most likely modes of action (MOA) for three lower molecular weight acrylates: (1) methyl acrylate (MA); (2) ethyl acrylate (EA); and (3) 2-ethylhexyl acrylate (2EHA). All three acrylates are generally

* Corresponding author.
E-mail address: ckirman@scipinion.com (C.R. Kirman).

https://doi.org/10.1016/j.yrtph.2023.105469
Received 12 June 2023; Received in revised form 8 August 2023; Accepted 10 August 2023
Available online 11 August 2023

considered to be non-genotoxic (Suh et al., 2018). Although epidemiology data are largely lacking for this group of chemicals, a variety of well conducted toxicology studies are available on these acrylates. A summary of the chronic studies is provided in Table 1. Multiple rodent cancer bioassays have been conducted for lower acrylates, including those for MA by the inhalation route (Reininghaus et al., 1991; JBRC, 2017), EA by the inhalation, oral, and dermal routes (DePass et al., 1984; Miller et al., 1985; NTP, 1986; Ghanayem et al., 1994), and 2EHA by the dermal route (DePass et al., 1985; Wenzel-Hartung et al., 1989; Mellert et al., 1994).

Low-to-moderate increases in tumor incidences have been noted in some cancer bioassays (Table 1). Point of contact tumors, including nasal tumors following inhalation (JBRC, 2017), forestomach tumors following oral gavage administration (NTP, 1986; but not via drinking water exposure; Borzelleca et al., 1964), and skin tumors following dermal contact (DePass et al., 1985), are noted in some studies. However, there are also multiple studies reporting no increase in point of contact tumors following chronic exposures to acrylates (JBRC, 2017; Reininghaus et al., 1991; Miller et al., 1985; Mellert et al., 1994). Several studies have reported weak increases in the incidence in systemic tumors, including combined soft tissue sarcomas (male rats; Reininghaus et al., 1991), combined hematopoietic/lymphoid cancers (male rats; Reininghaus et al., 1991), pituitary adenoma (female rats; Reininghaus et al., 1991), adrenal pheochromocytoma (female rats; JBRC, 2017), and thyroid follicular cell adenoma (female mice and male rats; Miller et al., 1985). These reports of systemic tumors are generally limited to a single study in one sex and rodent species/strain, with weak or non-monotonic dose-response relationships, are not statistically significant (e.g., $p > 0.05$) when incidence is not combined across tissue sites (e.g., soft tissue sarcomas), and/or the reported incidences are within or near historical control ranges. Furthermore, due to the rapid and extensive metabolism of acrylates (as reviewed in Suh et al., 2018), appreciable systemic doses of the parent chemicals are not expected to arise that could result in systemic tumor increases. Several of these tumor types have been evaluated more extensively in the published literature.

- *Rat Nasal tumors Produced by MA* - Wibbertmann et al. (2021) concluded that, based on the effects observed in the subchronic and chronic toxicity studies (JBRC, 2017), the highest test concentration of MA tested in rats of 160 ppm exceeded the maximum tolerated concentration (MTC). For this reason, the nasal tumors results observed at this concentration are of questionable relevance to human health risk assessment. Given that these exposure levels are much higher than would be tolerated by humans, the author concluded that the potential to pose a substantial cancer risk is implausible.
- *Mouse and Rat Forestomach Tumors Produced by EA* - Proctor et al. (2018) developed an adverse outcome pathway (AOP) for EA-induced forestomach tumors in rodents. Based on available evidence for EA, a sustained glutathione depletion is defined as a pre-molecular initiating event, epithelial cytotoxicity is defined as the critical initiating event, with supporting key events identified as increased cell proliferation resulting in sustained hyperplasia, ultimately resulting in the adverse outcome of forestomach tumors. Thompson et al. (2018) concluded that the weight of evidence supporting the MOA combined with the lack of a human tissue homologue makes it highly unlikely that EA exposure poses a cancer risk to human populations.

Table 1
Summary of rodent cancer bioassays for three lower acrylates.

Acrylate	Route of Exposure	Exposure regimen	Species/ Strain/Sex	Tumor sites of interest (Incidence in parentheses)[a]		Reference
				Point of Contact Tissues	Systemic Tissues	
Methyl acrylate	Inhalation	6 h/d, 5 d/wk for ~88–91 wks to 0, 2.5, 10, 40 ppm	Mouse/ B6D2F1/M	None	None	JBRC (2017)
			Mouse/ B6D2F1/F	None	None	JBRC (2017)
		6 h/day, 5 days/week for 2 years to 0, 15, 45, or 135 ppm	Rat/SD/M	None	Combined Soft tissue sarcoma (0/86, 4/86, 0/86, 6/86) Combined Hematopoietic and lymphatic cancers (0/86, 3/86, 7/86, 0/86)	Reininghaus et al., 1991
			Rat/SD/F	None	Pituitary adenoma (10/86, 21/86, 23/86, 9/86)	Reininghaus et al., 1991
		6 h/d, 5 d/wk for 2 yr to 0, 10, 40, 160 ppm	Rat/F344/M	Nasal (0/50, 0/50, 1/50, 6/50)	None	JBRC (2017)
			Rat/F344/F	Nasal (0/50, 0/50, 0/50, 2/50)	Adrenal pheochromocytoma (1/50, 1/50, 1/50, 4/50)	JBRC (2017)
Ethyl acrylate	Inhalation	6 h/d, 5 d/wk for 6–27 mo to 0, 25, 75, 225 ppm; 0 or 5 ppm	Mouse/ B6C3F1/M	None	Thyroid (2/121, 1/75, 0/76, 7/69)	Miller et al., (1985)
			Mouse/ B6C3F1/F	None	None	Miller et al., (1985)
			Rat/F344/M	None	Thyroid (1/120, 5/76, 2/75, 3/71)	Miller et al., (1985)
			Rat/F344/M	None	None	Miller et al., (1985)
	Oral gavage	5 d/wk for 103 wk to 0, 100, 200 mg/kg-d	Mouse/ B6C3F1/M	Forestomach (0/48, 5/47, 12/50)	None	NTP (1986)
			Mouse/ B6C3F1/F	Forestomach (1/50, 5/49, 7/48)	None	NTP (1986)
			Rat/F344/M	Forestomach (1/50, 18/50, 36/50)	None	NTP (1986)
			Rat/F344/F	Forestomach (1/50, 6/50, 11/50)	None	NTP (1986)
2-Ethylhexyl acrylate	Dermal	3x/wk for lifetime to 0 or 20 mg	Mouse/C3H/ HeJ/M	Skin (0/80, 4/40)	None	DePass et al., (1985)
		3x/wk for lifetime to 0, 2.5%, 21%, 86.5%	Mouse/C3H/ HeJ/M	Skin carcinoma (0/160, 0/80, 20/80)	None	Wenzel-Hartung et al., (1989)
		3x/wk for 2 yr to 0, 21.5%, 43%, 85%	Mouse/ NMRIBR/M	None	None	Mellert et al., (1994)

[a] Shading used to indicate the strength of the dose-response trend; light shading = weak (incidence increases of ~10% or less, and/or in a non-monotonic manner); medium shading (incidence increases 10–25% in a monotonic manner).

- *Mouse and Rat Thyroid Tumors Produced by EA* - Rosol and Witorsch (2021) assessed the data for thyroid tumors in mice and rats exposed to EA. The authors noted that the increased incidences while statistically significant ($p < 0.05$), were small and within the range of historical controls, and did not exhibit a consistent dose-response trend. Based on these observations, along with the fact that most of the thyroid tumors were benign, the authors concluded that these tumors were most likely random observations that were of questionable relevance to humans.
- *Mouse Skin Tumors Produced by 2EHA* – Elmets and Yusuf (2020) reviewed the carcinogenicity data for 2EHA reported that there are no reports of cancer in humans exposed to 2EHA. Furthermore, the authors concluded that the evidence from one strain of mouse (C3H/HeJ; DePass et al., 1984) was of questionable relevance for several reasons: (1) this strain of mouse has a mutation in Toll-like receptor 4 (TLR4) that impairs its immune responses; (2) there was a lack of rigorous histopathologic characterization of tumors that developed; (3) the doses of 2EHA tested in the study were high (i.e., above the maximum tolerated dose); and (4) the results of this study were not observed when in a second mouse strain (Mellert et al., 1994). Additionally, 2EHA was found to be not mutagenic in Chinese hamster V79 cells and did not induce micronuclei in human lymphocytes (Murphy et al., 2018).

Studies on the potential genotoxicity for these three acrylates are generally negative (as summarized in IARC, 2019; Suh et al., 2018), with limited positive findings that are associated with cytotoxic test concentrations.

The cancer weight of evidence based on the rodent cancer bioassay data for these three acrylates has been considered by several regulatory and health agencies (Table 2). IARC now considers all three acrylates to be "*possibly carcinogenic to humans*" (IARC, 2019). In contrast, NTP initially considered EA to be "*reasonably anticipated to be a carcinogen*" but was delisted in 1998 because (1) the forestomach tumors were seen only at high gavage doses that caused local irritation and subsequent cellular proliferation, (2) chronic human exposures to high concentrations are unlikely, and (3) no other tumors or systemic effects were observed (NTP, 1998). USEPA considered MA to be "*not classifiable as to human carcinogenicity*" (USEPA, 1990), and EA provisionally as "*not likely to be carcinogenic to humans*", but has not evaluated 2EHA with respect to its carcinogenicity (USEPA, 2014). These conclusions generally mirror those made by other agencies (e.g., ACGIH, 2023; Health Canada, 2011; European Chemicals Bureau, 2005).

This article presents the results of an expert panel-based review of the cancer WOE for three lower acrylates. The recommendations from this panel will be used to support quantitative risk assessment decisions. The methods and results of this expert panel engagement are described below.

Table 2
Cancer classifications for three lower acrylates.

Agency	Methyl Acrylate	Ethyl Acrylate	2-Ethylhexyl Acrylate
IARC (1987, 1999, 2019)	IARC, 1999: Not classifiable as to its carcinogenicity to humans (Group 3) 2019: Upgraded to possibly carcinogenic to humans (Group 2 B)	IARC, 1987: Possibly carcinogenic to humans (Group 2 B) 1999: No change from 1987 classification 2019: No change from 1987 classification	IARC, 1999: Not classifiable as to its carcinogenicity to humans (Group 3) IARC, 2019: Upgraded to possibly carcinogenic to humans (Group 2 B)
OEHHA (2023)	2021: Included on Prop 65 list	1989: Included on Prop 65 list	OEHHA, 2021: Included on Prop 65 list
NTP (1998)	–	1989: Reasonably anticipated to be a carcinogen 1998: Delisted	–
USEPA (1990, 2014)	1990: Not classifiable as to human carcinogenicity	2014: Not likely to be carcinogenic to humans (provisional)	–
ACGIH (2023)	A4: Not classifiable as a human carcinogen	A4: Not classifiable as a human carcinogen	
Health Canada (2011)		2011: Does not meet any of the criteria set out in section 64 of CEPA 1999	2018: Does not meet any of the criteria set out in section 64 of CEPA 1999
European Chemicals Bureau (2005)			2005: No conclusion could be drawn about the carcinogenic potential of 2-EHA. However, taking into account other information (e.g., lack of carcinogenic potential for metabolites acrylic acid, 2-ethylhexanol) there are no reasons to assume that 2-EHA should be considered as a carcinogenic substance

2. Methods and materials

2.1. Panel engagement

An expert panel was recruited and engaged utilizing the methods described in Kirman et al. (2019) as modified in Appendix A, with specific roles defined for the review sponsor, review manager (SciPinion; authors CRK, SMH), and independent expert panel members. Multiple design elements were included in this review to minimize potential sources of bias and groupthink, and to improve transparency of the review. These elements include the following: (1) a hybrid-blinding process, between single- and double-blinded was adopted for panel recruitment and engagement to minimize potential participation bias (2) the identities of experts were masked (e.g., labeled as Expert 1, Expert 2, etc.) during all online deliberations, (3) a multi-round, modified Delphi format was adopted to collect both independent and deliberative input from the topic experts in an effort to minimize potential groupthink; (4) panelists were specifically asked if there were any issues in the review material that warranted attention and discussion by the panel, in an attempt to minimize potential scope bias associated with charge questions that are too narrowly focused; (5) individual responses and comments from the panelists were recorded and are provided in their entirety (Appendix B) to provide precise measurements for the degree of consensus, ensure transparency, and minimize potential reporting bias; and (6) although individual responses are provided, they are attributed to panelists' anonymous display names (e.g., to Expert 1, Expert 2, etc.) rather than to specific panelist identities in an effort to provide psychological safety (*i.e.*, scientists should feel free to express their scientific opinions without fear of negative repercussions). Based on the robustness of the SciPinion review process, it was recently used to support a cancer weight of evidence decision by USEPA for an unrelated chemical (1,3-dichloropropene; USEPA, 1990).

Review material was defined by the review manager to include several recent reviews/publications as primary review material (IARC, 2019; Suh et al., 2018; Wiench et al., 2022), as well as underlying cancer bioassays and supporting material for the selected acrylates for the panel to consult as needed. Panelists were also given the opportunity to request access to additional publications/reports to support their review as needed.

2.2. Cancer weight of evidence framework

Multiple cancer weight of evidence classification frameworks are available from regulatory and health agencies (e.g., IARC, NIOSH, NTP, UN, USEPA), as summarized in ATSDR (2020). For this review, USEPA's Guidelines for Carcinogen Risk Assessment (USEPA, 2014) was adopted as the primary framework as this work is intended to support follow-up work on quantitative dose-response assessments within the United States. USEPA's guidance includes five possible weight of evidence classification descriptors.

- *Inadequate Information to Assess Carcinogenic Potential*
- *Not Likely to Be Carcinogenic to Humans*
- *Suggestive Evidence of Carcinogenic Potential*
- *Likely to Be Carcinogenic to Humans*
- *Carcinogenic to Humans*

In addition, the panelists were asked to consider a 2nd classification framework, United Nations' *Globally Harmonized System for Classification and Labelling of Chemicals* (UN 2011), which yielded similar conclusions of "carcinogen labeling not required" (see Appendix B).

2.3. Consensus analysis

For charge questions on cancer weight of evidence classification, the degree of consensus among reviewers was assessed with precision using the consensus metrics of Tastle and Wierman (2007):

$$Consensus = 1 + \sum_{i=1}^{n} p_i \, log_2\left(1 - \frac{|X_i - \mu_x|}{d_x}\right)$$

where p is the probability (frequency) for the answer option i, μ_x is the mean index value, X_i is an index for graded or Likert answer option i (e.g., "inadequate evidence" = 0, "not likely carcinogenic" = 1, "suggestive evidence" = 2, "likely carcinogenic" = 3, "carcinogenic" = 4), d_x is the width of the index values (X_{max}–X_{min}), n is the number of answer options. The value for the consensus metric can range from a value of "0" when there is a complete lack of consensus (*i.e.*, when equal numbers of panelists select the two extreme answer options) to a value of "1" when there is complete consensus (all panel members select the same answer option). All summary statistics, calculations, and figures were prepared using Microsoft Excel (version 15.67).

3. Results

3.1. Panel composition

The panel consisted of seven scientists with expertise in cancer bioassays, mode of action, risk assessment, and weight of evidence. Demographics, affiliations, and expertise metrics for this panel are as follows.

- •Advanced Degrees: PhD (7), MD (1)
- •Mean years of experience: 41 ± 4 years
- •Mean number of publications: 138 ± 97
- •Country of residence: Canada (1), Germany (1), Netherlands (1), United States (4)
- Current sector of employment: Academia (2), Consulting (2), Industry (1), Retired/Government (1), Retired/Industry (1)

3.2. Mode of action

Mode of action (MOA) information is important to key decisions made in cancer risk assessment including those related to human relevance including identification of potentially susceptible populations, calculation of chemical specific adjustment factors/dose measures, and low-dose extrapolation methods used to estimate cancer potency (USEPA, 2014). For the three lower acrylates, confidence in the weight of evidence for potential cancer MOAs was rated on a scale of "-5" (i.e., there is strong refuting evidence) to "0" (i.e., evidence is equivocal) to "+5" (i.e., there is strong supporting evidence) (Fig. 1).

Overall, panel confidence was highest for an MOA involving "Increased cell replication by cytotoxicity" (mean confidence scores ranging from +2.3 to +3.0, reflecting a moderate degree of support). These results reflect the strong evidence of non-neoplastic effects (e.g., irritation, inflammation, hyperplasia, metaplasia) occurring at the point of contact for all three routes of exposure. These non-neoplastic local lesions were found to occur at lower (and similar) concentrations than were the observed tumors (Wibbertmann et al., 2021; Wenzel-Hartung et al., 1989). In addition, observations of reversibility of non-neoplastic effects and lack of tumor response in stop-exposure studies (Miller et al., 1985; Wenzel-Hartung et al., 1989; Ghanayem et al., 1994) were noted as an important consideration. Confidence in the other MOAs ranged from equivocal to strongly refuted, with the following relative ranking of mean scores. An MOA involving "Indirect genotoxicity" (mean scores of −1.0 to −0.8) was noted as being at least biologically plausible given the ability of the acrylates to deplete tissue glutathione at high concentrations. Evidence supporting either "Other" (mean scores of −2.0 to +0.3), "Immune system mediated" (mean scores of −2.8 to −1.7), and "Increased cell replication by receptor binding" (mean scores of −3.5 to −2.4) are generally negative although based on limited data (e.g., high throughput screening assays). Because of their toxicological profiles, chemical properties, as well as, biological plausibility, the relative weight of evidence for the cytotoxicity/regenerative MOA is considered with more certainty to explain the primary effects of the acrylates. Direct genotoxicity (mean scores of −3.9 to −4.1) is considered moderately-to-strongly refuted by the panelists based on largely negative results obtained for genotoxicity studies, with limited positive results associated with cytotoxic test concentrations, or non-relevant exposure routes (e.g., injection). It is recognized that this categorization of individual MOAs here represents a simplification of the underlying biology as they may not be independent of one another, may operate in combination, and/or operate in different tissue sites and/or dose levels. The reader is referred to Appendix B for explanatory text provided by the panelists for charge questions on MOA.

3.3. Use of available tumor datasets in risk assessment

As discussed above (see Introduction) there are multiple data sets that could potentially be used to support human health risk assessment for the three lower acrylates (Table 1). Information on MOA can be used to inform how these data should be used (e.g., qualitatively, quantitatively, or not at all). The panelists' conclusions on this topic are summarized in Table 3.

For most tumor data sets, a majority of the panelists indicated that they should either not be used in human health risk assessment or should only be used qualitatively. Factors that influenced this decision include.

1. There is no human tissue counterpart (e.g., rodent forestomach).
2. Toxicokinetic factors, such as gavage exposures that yield tissue dose rates that are much greater than expected for drinking water or other exposures. This difference may explain the lack of forestomach tumors in rats exposed to methyl methacrylate or ethyl acrylate via drinking water (Borzelleca et al., 1964). In addition, longer residence times are expected for chemicals in rodent forestomach compared to human esophagus.
3. The dose-response relationships for forestomach tumors exhibited non-monotonic behaviors and/or within historical control ranges for common rodent tumors.
4. The magnitude of the dose/concentration (e.g., exceeding the maximum tolerated dose) was also a factor considered for human

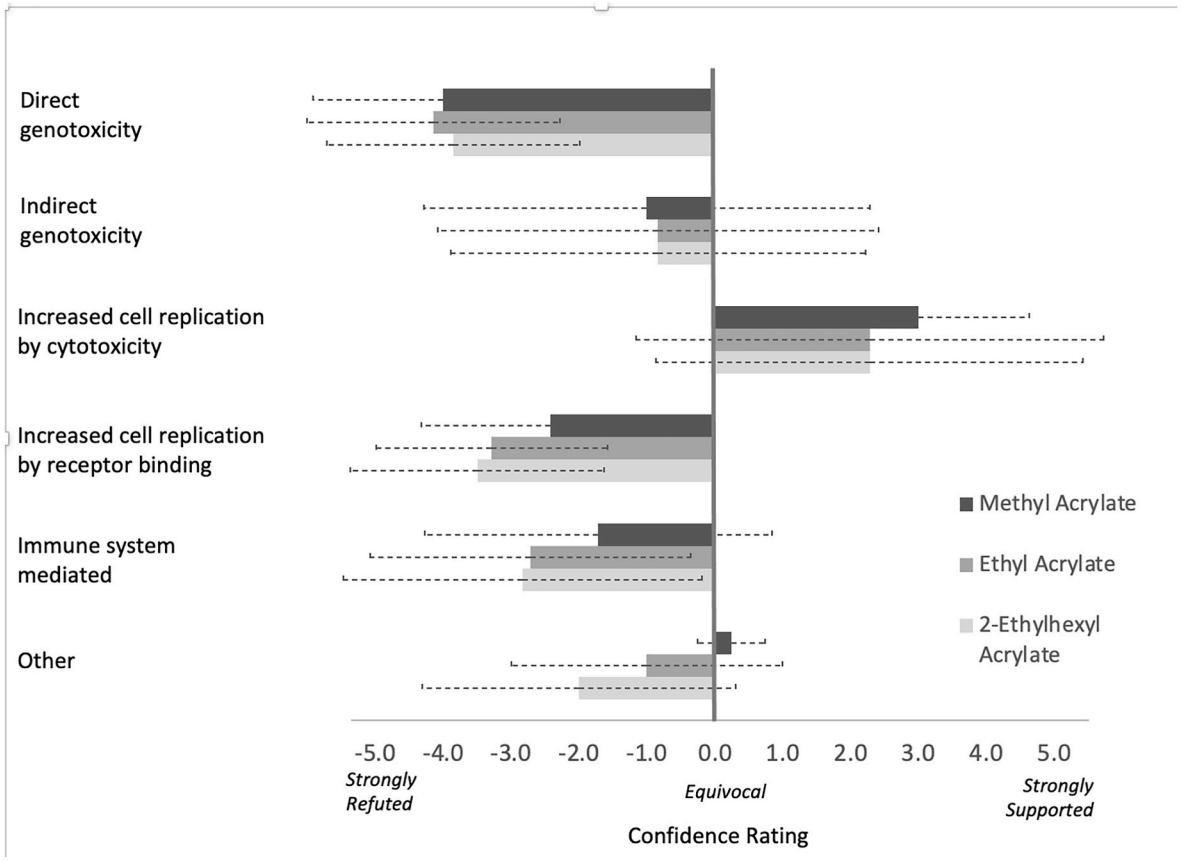

Fig. 1. Panel Confidence in Potential MOAs for the Carcinogenic Effects of Three Lower Acrylates in Rodent Studies (bars indicate arithmetic mean, error bars indicate standard deviation; This refers to questions 1.3, 2.3, 3.3 in Appendix B).

relevance. Some panelists felt this factor should be considered separately from human relevance determination.

The only tumor data sets that garnered minimal support (e.g., from a single panel member) for use in quantitative potency estimates was for data sets that reported no increase in tumors at the highest dose tested. Review of the explanatory text for pertinent charge questions (1.4, 2.4, and 3.4 in Appendix B) revealed a strong preference by many panel members to rely upon data sets for non-neoplastic endpoints/precursor lesions to support quantitative, human health risk assessment for the three acrylates.

3.4. Cancer weight of evidence

Panelists were asked to classify the cancer weight of evidence for the three lower acrylates as well as indicate their degree of confidence in their conclusion (Fig. 2).

For all three chemicals, a majority of the panelists concluded that the WOE supported a classification of "*Not likely to be carcinogenic to humans*". The basis for this conclusion includes: (1) observations for irritation effects specifically at the point of entry; (2) evidence supporting a non-genotoxic MOA consistent with cytotoxicity/regenerative proliferation; (3) observations of concentration-dependent responses consistent with a nonlinear/threshold dose-response relationship; and (4) expectations that humans would not be exposed to the levels causing chronic inflammation and cytotoxicity. Specific rationales from individual panel members for supporting this conclusion are provided in Appendix B. The degree of consensus was high, with consensus scores ranging from 0.84 to 0.91 (out of a maximum score of 1), as was the degree of confidence in this classification (mean confidence scores ranging from 7.7 to 8.7 out of a maximum score of 10). Consensus and confidence scores were slightly higher for EA compared to corresponding values for the other two acrylates. A panelist in the minority who indicated "*Suggestive evidence of carcinogenic potential*" noted that this classification should possibly include the qualifier "*at high doses*" in one case. In another case a panelist felt that the increases in systemic tumors (Table 1) could not be completely rejected. A similar cancer WOE classification (i.e., carcinogen labeling not required) was obtained when the panelists were asked to consider an alternative framework (United Nations' Globally Harmonized System for Classification and Labelling of Chemicals, UN 2011; see Appendix B).

3.5. Need for cancer potency estimation

One of the goals of this work was to collect input from the panel to support decisions made in quantitative human health risk assessments for the lower acrylates (in prep). Along these lines, the panelists were asked whether cancer potency estimates/safety values should be derived for the three lower acrylates (Fig. 3).

A clear majority of panelists (71–86%) do not feel a cancer potency/safety value is required for these acrylates. These conclusions generally mirror those from the panel for cancer weight of evidence classification (i.e., if a conclusion of "Not likely to be carcinogenic to humans" is reached, then a cancer value is not needed).

4. Discussion and conclusions

An expert panel was engaged to evaluate the cancer WOE for three lower acrylates, MA, EA, and 2EHA. Genotoxicity studies for this group of chemicals are generally negative, with limited positive associated with cytotoxicity. Per OECD guidelines (OECD, 2015), the highest test concentration should not exceed 55 ± 5%, and care should be taken in

Table 3
Recommendations for use of tumor data sets for several lower acrylates (questions 1.4, 2.4, 3.4 in Appendix B)[a].

Acrylate	Data Set	Percent of Panelists (n = 7)[a]			
		Not used (e.g., not relevant to human health)	Used qualitatively only (e.g., cancer classification)	Used qualitatively and quantitatively (e.g., estimate potency)	Other
MA	No increase in tumors in male mice (JBRC, 2017)		71%	14%	14%
	No increase in tumors in female mice (JBRC, 2017)		71%	14%	14%
	Point-of-contact tumors (nasal cavity) in male rats (JBRC, 2017)	57%	29%		14%
	Point-of-contact tumors (nasal cavity) in female rats (JBRC, 2017)	71%	14%		14%
	Systemic tumors (soft tissue sarcoma) in male rats (Reininghaus et al., 1991)	43%	29%		29%
	Systemic tumors (lymphohematopoietic cancers) in male rats (Reininghaus et al., 1991)	43%	29%		29%
	Systemic tumors (pituitary gland adenomas) in female rats (Reininghaus et al., 1991)	43%	29%		29%
	Systemic tumors (adrenal pheochromocytomas) in female rats (JBRC, 2017)	57%	14%		29%
	Other (please specify)				29%
EA	No increase in tumors in female rats (Miller et al., 1985)		71%	14%	14%
	Point-of-contact tumors (forestomach) in male mice (NTP, 1986)	57%	14%	14%	14%
	Point-of-contact tumors (forestomach) in female mice (NTP, 1986)	57%	29%		14%
	Point-of-contact tumors (forestomach) in male rats (Ghanayem et al., 1994)	57%	29%		14%
	Point-of-contact tumors (forestomach) in female rats (Ghanayem et al., 1994)	43%	14%		43%
	Systemic tumors (thyroid) in male mice (Miller et al., 1985)	43%	29%		29%
	Systemic tumors (thyroid) in male rats (Miller et al., 1985)	43%	29%		29%
	Other (please specify)	14%			29%
2EHA	No increase in skin tumors in male mice (Mellert et al., 1994)	14%	71%	14%	
	Point-of-contact tumors (skin) in male mice (Depass et al., 1985)	57%	29%		14%
	Point-of-contact tumors (skin) in male mice (Wenzel-Hartung et al., 1989)	57%	43%		
	Other (please specify)	14%			14%

[a] Shading indicates the relative proportion of panelists selecting a response.

interpreting positive results only found in the higher end of this 55 ± 5% cytotoxicity range. Observations for carcinogenicity from rodent cancer bioassays are limited. Weak increases in systemic tumors (Table 1) may not be treatment related and appear to be of questionable relevance to human health. Increases in tumors observed at the point of contact in some studies (Table 1), while clearly treatment related, also appear to be of questionable relevance to human health based on MOA considerations. The overall conclusions of this expert panel can be summarized as follows.

(1) The MOA for point of contact tumors observed in rodent cancer bioassays that is best supported by available data involves increased cell replication by cytotoxicity and regenerative proliferation;
(2) The WOE supports a cancer classification of "*Not likely to be carcinogenic to humans*" based upon USEPA (2014) classification framework, and that carcinogen labeling is not required under the UN Global Harmonization System (UN 2011);
(3) A quantitative estimate of cancer potency based on rodent tumor data is not required for these chemicals; and
(4) Human health risk assessment for these chemicals should instead rely on non-cancer, precursor endpoints at the point of contact (e.g., hyperplasia).

The degree of consensus across panel members in these conclusions is considered high. The relevance of some tumor types to human health e.g., rodent forestomach tumors, adrenal pheochromocytomas) was questioned by some panel members, a conclusion that is supported by other researcher (Proctor et al., 2007; Adams et al., 2008). A similar conclusion has been reached in the published literature for rodent adrenal pheochromocytoma (Greim et al., 2009), although this issue was not specifically discussed by the panel.

The evidence for each of the three structurally similar acrylates considered individually is strengthened when the totality of the evidence is considered as a group, which is consistent with read-across approaches (OECD, 2014). Read-across is considered appropriate for these acrylates since they share common metabolic pathways (i.e., extensive and rapid carboxylesterase hydrolysis to a common metabolite, acrylate that is not considered to be carcinogenic), and mode of action (i.e., increased cell replication due to cytotoxicity). In addition to conclusions on WOE and MOA for these chemicals, the panelists identified potential data needs (charge questions 1.7, 2.7, and 3.7 in Appendix B), which could be used to increase confidence in their assessments. For example, one panel member suggested that additional studies to provide data that could be used to address modified Bradford-Hill criteria (e.g., essentiality/reversibility, dose-response concordance, biological coherence, biological plausibility, strength of association, temporal concordance, analogy) for hypothesized key events could improve confidence in the proposed MOA. Panelists noted some inconsistencies in the evidence for the role of GSH depletion.

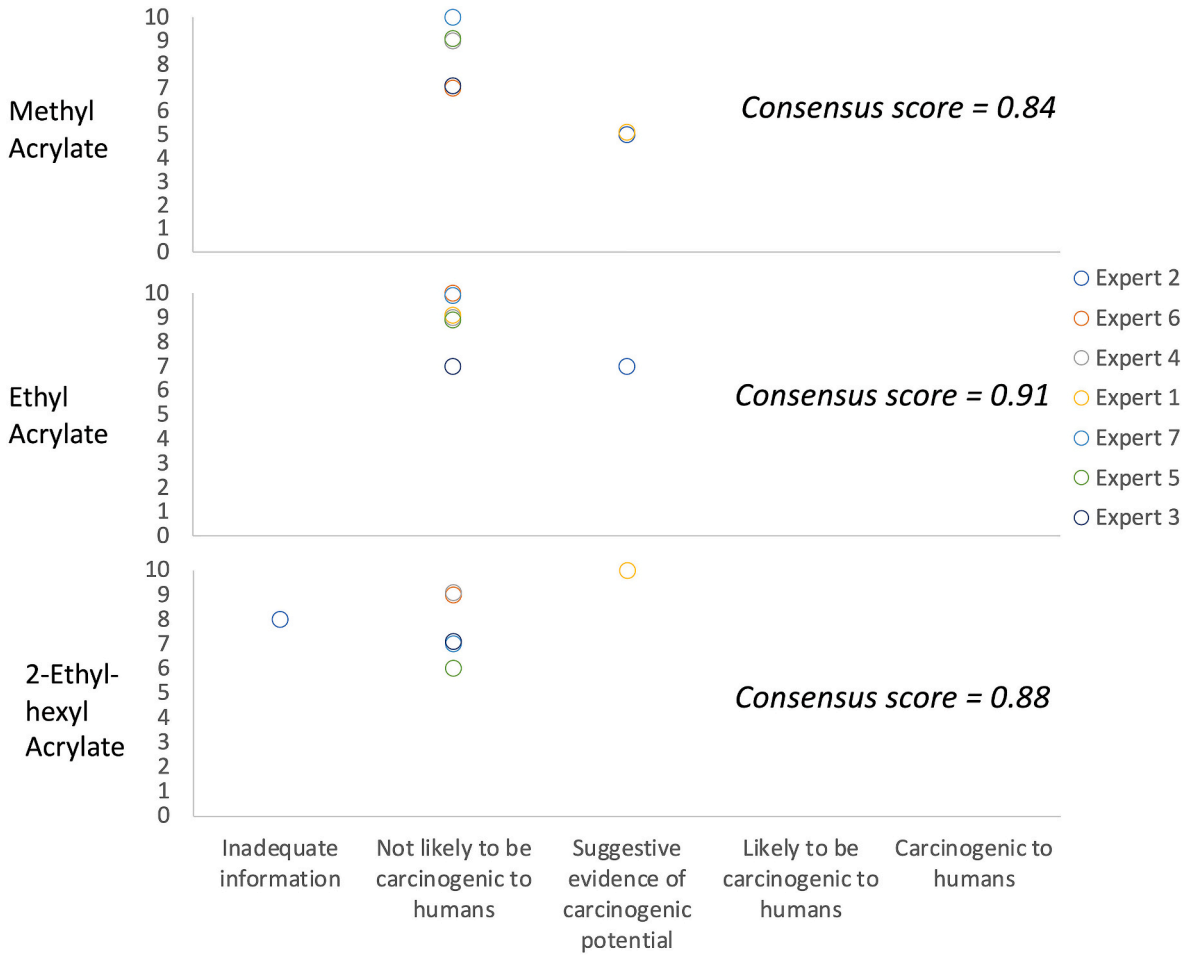

Fig. 2. Cancer Weight of Evidence Classification vs. Confidence Score (1 = lowest, 10 = highest) for Three Lower Acrylates (This refers to questions 1.5, 1.6, 2.5, 2.6, 3.5, 3.6 in Appendix B).

Although these data are not considered essential for their conclusions on MOA, additional data on the role of GSH depletion in the point of contact effects and resolution of potential inconsistencies could improve MOA confidence. Additional toxicokinetic data and modeling of the residual levels of acrylates reaching systemic tissues (i.e., surviving first-pass metabolism at the point of contact) would be helpful for interpreting the biological plausibility of systemic tumor formation. There was some discussion among panelists on the use of exposure information in human relevance and cancer weight of evidence classification decisions. USEPA's guidelines do specifically permit consideration for exposure information in classification determinations in stating that "*convincing evidence that carcinogenic effects are not likely below a defined dose range can be considered for the classification Not likely to be carcinogenic to humans*" (USEPA, 2014, p.2-58). While limited information indicates that human exposures to acrylates (Suh et al., 2018; IARC, 2019) are well below those eliciting a tumor response in the cancer bioassays, updated data on the magnitude of human exposures (occupational and in the general population) would serve to bolster this conclusion.

Although the size of the panel (n = 7) does not permit a rigorous statistical analysis, some limited comparisons can be made across panel subgroups. For example, WOE indices averaged across the three acrylates can be compared across panel subgroups (note, a higher mean index value would reflect a shift to the right in Fig. 2 when compared to lower values). Based on this comparison, no significant differences were noted between U.S. panelists (n = 4; mean = 1.2 ± 0.4) vs. non-U.S. panelists (n = 3; mean = 1.1 ± 0.4), or between panelists with current/past industry employment (n = 3; mean = 1.2 ± 0.4) vs. panelists with no industry employment (n = 4; mean = 1.1 ± 0.5). The latter observation is consistent with those of Kirman et al. (2019), which did not find a significant difference in panelist responses when stratified by sector of employment.

The goal of this work is to provide an independent assessment of the cancer weight of evidence data available for three lower acrylates. A panel of topic experts was engaged in reviewing summary material, consulting primary studies as needed, and providing their conclusions and recommendations. The panel's conclusions are in sharp contrast to those of IARC, and are more in line with a classification of Group 3 (Not classifiable as to its carcinogenicity to humans) for these acrylates. The panel's conclusions are consistent with those made previously by other agencies (USEPA, 1990; NTP, 1998; ACGIH, 2023; Health Canada, 2011; European Chemicals Bureau, 2005; Table 2). Confidence in the panel conclusions is considered high, and will serve as valuable input to decisions made in the quantitative dose-response assessments for these chemicals.

Funding body information

This work was funded by BASIC ACRYLIC MONOMER

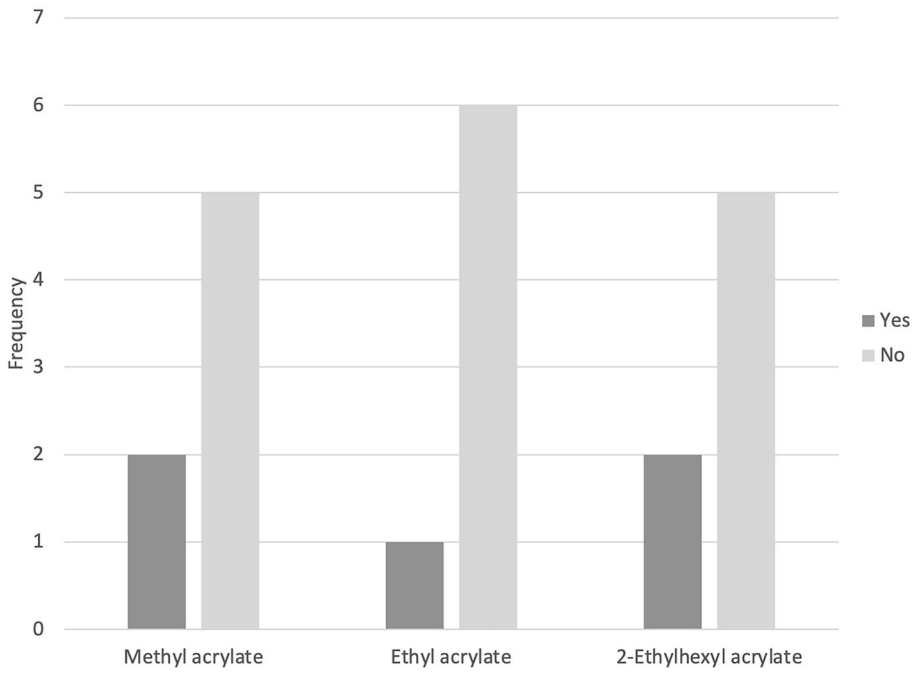

Fig. 3. Should Cancer Potency Estimates/Safety Values (e.g., No-Significant-Risk-Level for Prop65) Be Derived for Three Lower Acrylates (This refers to questions 5.2, 5.4, 5.6 in Appendix B).

MANUFACTURERS, INC., 4719 Eskerhills, Williamsburg, VA 23,188.

CRediT authorship contribution statement

C.R. Kirman: Conceptualization, Methodology, Writing – original draft, Revisions, Project administration. **P.J. Boogaard:** Expert Panelist, Writing – review & editing. **J.S. Bus:** Expert Panelist, Writing – review & editing. **V.L. Dellarco:** Expert Panelist, Writing – review & editing. **L.R. DePass:** Expert panelist, Writing – review & editing. **B.R. Stern:** Expert Panelists, Writing – review & editing. **S.M. Hays:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The project was financed by the Basic Acrylic Monomer Manufacturers (BAMM), Inc., Contract 072,522.

The authors listed on the cover page certify that they have no conflict of interest to declare. Authors SMH and CRK are independent consultants and are owners of SciPinion. The paper was subjected to a review for completeness and clarity by members of BAMM and are employed by commercial companies with a financial interest in the subject matter, but were not permitted to revise opinions or conclusions.

Data availability

Raw response data from panel is included in Appendix B.

Acknowledgements and disclaimers

We would like to thank the seven selected experts for contributing their expertise and time to this panel and for their thoughtful comments on the draft manuscript [Authors PJB, VLD, BRS, LRD, JSB], as well as panelists Drs. Dieter Schrenk, (University of Kaiserslautern) and Bette Meek (University of Ottawa). The experts were notified during recruitment that their identities would be made publicly available following the completion of the peer review, and that the findings might be published in a peer reviewed manuscript. Their collective input and rationale for their positions are made fully transparent in Appendix B. Moreover, it is important to recognize that all panelists participated in the review as independent experts rather than as representatives of their employers and were unaware of the sponsor or fellow panelists' identities until they reviewed this manuscript.

The panel engagement presented in this manuscript was funded by *the Basic Acrylic Monomer Manufacturers, Inc.* (the Sponsor). The science that was peer reviewed included studies conducted by the Sponsor and their contractors. The authors of this paper (CRK and SMH) had complete control of the conduct of the peer reviews and the content of this manuscript. The Sponsor was provided an opportunity to review this manuscript to ensure clarity and completeness. The authors, CRK and SMH are owners of SciPinion and thus have a financial interest in the content of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2023.105469.

References

ACGIH. Online database accessed May 19, 2023. https://www.acgih.org/data-hub/.

Adams, T.B., Gavin, C.L., Taylor, S.V., Waddell, W.J., Cohen, S.M., Feron, V.J., Goodman, J., Rietjens, I.M., Marnett, L.J., Portoghese, P.S., Smith, R.L., 2008. The FEMA GRAS assessment of alpha,beta-unsaturated aldehydes and related substances used as flavor ingredients. Food Chem. Toxicol. 46 (9), 2935–2967. https://doi.org/10.1016/j.fct.2008.06.082. Epub 2008 Jul 3. Erratum in: Food Chem Toxicol. 2009 Oct;47(10):2686. PMID: 18644420.

ATSDR, 2020. Cancer Classification Systems. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Borzelleca, J.F., Larson, P.S., Hennigar Jr., G.R., Huf, E.G., Crawford, E.M., Smith Jr., R. B., 1964. Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. Toxicol. Appl. Pharmacol. 6, 29–36. https://doi.org/10.1016/0041-008x(64)90019-5. PMID: 14105896.

Brüning, T., Bartsch, R., Bolt, H.M., Desel, H., Drexler, H., Gundert-Remy, U., Hartwig, A., Jäckh, R., Leibold, E., Pallapies, D., Rettenmeier, A.W., Schlüter, G., Stropp, G., Sucker, K., Triebig, G., Westphal, G., van Thriel, C., 2014. Sensory irritation as a basis for setting occupational exposure limits. Arch. Toxicol. 88 (10), 1855–1879. https://doi.org/10.1007/s00204-014-1346-z. Epub 2014 Sep 3. PMID: 25182421; PMCID: PMC4161939.

DePass, L.R., Maronpot, R.R., Weil, C.S., 1985. Dermal oncogenicity bioassays of monofunctional and multifunctional acrylates and acrylate-based oligomers. J. Toxicol. Environ. Health 16 (1), 55–60. https://doi.org/10.1080/15287398509530718. PMID: 4068056.

DePass, L.R., Fowler, E.H., Meckley, D.R., Weil, C.S., 1984. Dermal oncogenicity bioassays of acrylic acid, ethyl acrylate, and butyl acrylate. J. Toxicol. Environ. Health 14 (2–3), 115–120. https://doi.org/10.1080/15287398409530566. PMID: 6153064.

Elmets, C.A., Yusuf, N., 2020. Murine skin carcinogenesis and the role of immune system dysregulation in the tumorigenicity of 2-ethylhexyl acrylate. Biomed. Hub 5 (2), 958–973. https://doi.org/10.1159/000508295. PMID: 33564662; PMCID: PMC7841744.\.

European Chemicals Bureau, 2005. European Union Risk Assessment Report. 2-Ethylhexyl Acrylate. European Commission, Luxembourg. CAS No. 103-1107. EINECS No: 203-080-7.

Greim, H., Hartwig, A., Reuter, U., Richter-Reichhelm, H.B., Thielmann, H.W., 2009. Chemically induced pheochromocytomas in rats: mechanisms and relevance for human risk assessment. Crit Rev Toxicol 39, 695–718. https://doi.org/10.1080/10408440903190861. PMID: 19743946.

Ghanayem, B.I., Sanchez, I.M., Matthews, H.B., Elwell, M.R., 1994. Demonstration of a temporal relationship between ethyl acrylate-induced forestomach cell proliferation and carcinogenicity. Toxicol. Pathol. 22 (5), 497–509. https://doi.org/10.1177/019262339402200504. PMID: 7899778.

Health Canada, 2011. Screening Assessment for the Challenge. 2-Propenoic Acid, Ethyl Ester (Ethyl Acrylate). Chemical Abstracts Service. Environment Canada Health, Canada. Registry Number 140-88-5.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2019. Isobutyl Nitrite, β-Picoline, and Some Acrylates. Lyon (FR). International Agency for Research on Cancer. PMID: 32520473.

IARC, 1999. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. In: Reevaluation of Some Organic Chemicals, Hydrazine, and Hydrogen Peroxide, vol. 71. World Health Organization International Agency for Research on Cancer Lyon, France.

IARC, 1987. IARC monographs on the evaluation of carcinogenic risks to humans, supplement 7. In: Overall Evaluations of Carcinogenicity: an Updating of IARC Monographs Volumes 1 to 42, p. 63. Lyon.

Japan Bioassay Research Center, 2017. Summaries of Inhalation Carcinogenicity Studies of Methyl Acrylate in F344 Rats and B6D2F1 Mice. Japan Organization of Health and Safety, Japan (Available from: the Ministry of Health, Labour and Welfare of Japan. [Japanese]).

Kirman, C.R., Simon, T.W., Hays, S.M., 2019. Science peer review for the 21st century: assessing scientific consensus for decision-making while managing conflict of interests, reviewer and process bias. Regul. Toxicol. Pharmacol. 103, 73–85. https://doi.org/10.1016/j.yrtph.2019.01.003. Epub 2019 Jan 8. PMID: 30634024.

Mellert, W., Kühborth, B., Gembardt, C., Munk, R., 1994. 2-year carcinogenicity study in the male NMRI mouse with 2-ethylhexyl acrylate by epicutaneous administration. Food Chem. Toxicol. 32 (3), 233–237. https://doi.org/10.1016/0278-6915(94)90195-3. PMID: 8157217.

Miller, R.R., Young, J.T., Kociba, R.J., Keyes, D.G., Bodner, K.M., Calhoun, L.L., Ayres, J. A., 1985. Chronic toxicity and oncogenicity bioassay of inhaled ethyl acrylate in Fischer 344 rats and B6C3F1 mice. Drug Chem. Toxicol. 8 (1–2), 1–42. https://doi.org/10.3109/01480548509011632. PMID: 4017897.

Murphy, S., Ellis-Hutchings, R., Finch, L., Welz, S., Wiench, K., 2018. Critical evaluation of 2-ethylhexyl acrylate dermal carcinogenicity studies using contemporary criteria. Toxicol. Lett. 294, 205–211. https://doi.org/10.1016/j.toxlet.2018.05.016. Epub 2018 May 15. PMID: 29775721.

NTP, 1986. NTP technical report on the carcinogenesis studies of ethyl acrylate (CasNo. 140-88-5) in F33/N rats and B6C3F1 mice (gavage studies). In: National Toxicology Program December 1986. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NTP TR 259 NIH Publication No. 87–2515.

NTP, 1998. Report on Carcinogens Background Document for Ethyl Acrylate. December 2 -3, 1998 Meeting of the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee.

OECD, 2014. Guidance on grouping of chemicals. In: Series on Testing & Assessment No. 194, second ed. ENV/JM/MONO(2014), p. 4.

OECD, 2015. Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines. https://www.oecd.org/env/ehs/testing/Draft%20Guidance%20Document%20on%20OECD%20Genetic%20Toxicology%20Test%20Guidelines.pdf.

OEHHA, 2021. Title 27, California Code of Regulations. ARTICLE 7.

OEHHA, 2023. Chemicals KNOWN to the state to cause cancer or reproductive toxicity. January 27, 2023.

Proctor, D.M., Gatto, N.M., Hong, S.J., Allamneni, K.P., 2007. Mode-of-action framework for evaluating the relevance of rodent forestomach tumors in cancer risk assessment. Toxicol. Sci. 98 (2), 313–326. https://doi.org/10.1093/toxsci/kfm075. Epub 2007 Apr 10. PMID: 17426108.

Proctor, D.M., Suh, M., Chappell, G., Borghoff, S.J., Thompson, C.M., Wiench, K., Finch, L., Ellis-Hutchings, R., 2018. An Adverse Outcome Pathway (AOP) for forestomach tumors induced by non-genotoxic initiating events. Regul. Toxicol. Pharmacol. 96, 30–40. https://doi.org/10.1016/j.yrtph.2018.04.016. Epub 2018 Apr 21. PMID: 29684431.

Reininghaus, W., Koestner, A., Klimisch, H.J., 1991. Chronic toxicity and oncogenicity of inhaled methyl acrylate and n-butyl acrylate in Sprague-Dawley rats. Food Chem. Toxicol. 29 (5), 329–339. https://doi.org/10.1016/0278-6915(91)90204-k. PMID: 2060891.

Rosol, T.J., Witorsch, R.J., 2021. Ethyl acrylate (EA) exposure and thyroid carcinogenicity in rats and mice with relevance to human health. Regul. Toxicol. Pharmacol. 124, 104961 https://doi.org/10.1016/j.yrtph.2021.104961. Epub 2021 May 18. PMID: 34015422.

Suh, M., Proctor, D., Chappell, G., Rager, J., Thompson, C., Borghoff, S., Finch, L., Ellis-Hutchings, R., Wiench, K., 2018. A review of the genotoxic, mutagenic, and carcinogenic potentials of several lower acrylates. Toxicology 402–403, 50–67. https://doi.org/10.1016/j.tox.2018.04.006. Epub 2018 Apr 22. PMID: 29689363.

Tastle, W.J., Wierman, M.J., 2007. Consensus and dissention: a measure of ordinal dispersion. Int. J. Approx. Reason. 45, 531–545.

Thompson, C.M., Suh, M., Proctor, D.M., Chappell, G., Borghoff, S., Ellis-Hutchings, R., Wiench, K., Finch, L., 2018. Assessment of the mode of action underlying development of forestomach tumors in rodents following oral exposure to ethyl acrylate and relevance to humans. Regul. Toxicol. Pharmacol. 96, 178–189. https://doi.org/10.1016/j.yrtph.2018.05.006. Epub 2018 May 5. PMID: 29738809.

UN, 2011. Globally Harmonized System of Classification and Labelling of Chemicals (GHS), fourth ed. United Nations, New York and Geneva. Available from: https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf.

USEPA, 1990. Integrated Risk Information System (IRIS). United States Environmental Protection Agency. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris/.

USEPA, 2014. Provisional Peer-Reviewed Toxicity Values for Ethyl Acrylate (CASRN 140-88-5). Superfund Health Risk Technical Support Center National Center for Environmental Assessment Office of Research and Development U.S. Environmental Protection Agency Cincinnati. OH 45268. EPA/690/R-14/005F.

Wenzel-Hartung, R.P., Brune, H., Klimisch, H.J., 1989. Dermal oncogenicity study of 2-ethylhexyl acrylate by epicutaneous application in male C3H/HeJ mice. J. Cancer Res. Clin. Oncol. 115 (6), 543–549. https://doi.org/10.1007/BF00391355. PMID: 2606929.

Wibbertmann, A., Bitsch, A., Kuper, C.F., 2021. Comprehensive analysis of chronic rodent inhalation toxicity studies for methyl acrylate with attention to test conditions exceeding a maximum tolerated concentration. Regul. Toxicol. Pharmacol. 122, 104900 https://doi.org/10.1016/j.yrtph.2021.104900. Epub 2021 Feb 24. PMID: 33636299.

Wiench, K., Honarvar, N., Fabian, E., Landsiedel, R., Hindle, S., Finch, L., 2022. Critical Review on the Assessment on the Tumorigenic Effects of Some Lower-Chain Acrylates. Toxicologist.