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Derivation of no significant risk levels for three lower acrylates: Conclusions and recommendations from an expert panel☆,☆☆

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ABSTRACT

A panel of toxicology, mode of action (MOA), and cancer risk assessment experts was engaged to derive no-significant-risk-levels (NSRLs) for three lower acrylates: methyl acrylate (MA), ethyl acrylate (EA), and 2-ethylhexyl acrylate (2EHA) using the best available science, data, and methods. The review was structured as a five-round, modified Delphi format, a systematic process for collecting independent and deliberative input from panel members, and it included several procedural elements to reduce potential sources of bias and groupthink. Input from the panel for key decisions in the dose-response assessments resulted in NSRL values of 530 μg/day (330–800 μg/day), 640 μg/day (280–670 μg/day), and 1700 μg/day (1300–2700 μg/day) for MA, EA, and 2EHA, respectively. Novel to this approach were the use of nonneoplastic lesions reported at point of contact where tumors have been reported in laboratory rodents, along with nonlinear extrapolation to low doses (uncertainty factor approach) based upon panel recommendations. Confidence in these values is considered medium to high for exposures applied to the routes of exposure tested (inhalation for MA and EA, dermal for 2EHA), but confidence is considered lower when applied to other routes of exposure.

1. Introduction

Lower acrylate monomers, such as methyl acrylate (MA), ethyl acrylate (EA) and 2-ethylhexyl acrylate (2EHA) serve as building blocks for polymers and copolymers that are used in a variety of products (e.g., adhesives, cosmetic products, industrial coatings, leather finishes, packaging, paint formulations, plastics, synthetic flavoring, and textiles; Suh et al., 2018). These three lower acrylates have been assessed for potential carcinogenicity in multiple animal bioassays (as summarized in IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2019; Suh et al., 2018; Kirman et al., 2023). IARC (2019) has classified these three chemicals as "*Possibly Carcinogenic to Humans*" based on their conclusion of "sufficient" evidence of carcinogenicity in animals. Thus, the State of California is required to add them to the Proposition 65 list (California Labor Code Section 6382(b)(1)), which in turn can prompt the derivation of No-Significant-Risk-Level (NSRL) values. NSRLs are defined by the State of California as "*the level of exposure to a listed chemical which, assuming daily exposure at that level, poses no significant risk*" (California Code of Regulations, Title 27, Article 7). They are typically expressed in terms of a daily intake or exposure rate (i.e., in terms of ug chemical per day). This regulation recommends methods for the derivation of NSRL values on endpoint (tumor response), dosimetry (allometric scaling), dose-response modeling (multistage model), low-dose extrapolation (linear), and acceptable risk level (1×10^{-5}).

In contrast to IARC's conclusions on the cancer weight of evidence for lower acrylates, other health agencies (USEPA, NTP, OEHHA, ECHA) have reached different conclusions (as reviewed in Kirman et al., 2023).

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Recently, an independent panel of experts (Kirman et al., 2023; hereafter referred to as Panel 1) reviewed available information related to the carcinogenic potential of these three acrylic monomers and yielded the following conclusions:

(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; and furthermore, a direct genotoxic MOA was strongly refuted based on the available evidence for these three acrylates, which have been well-tested in multiple genotoxicity assays;
(2) The WOE supports a cancer classification of "*Not likely to be carcinogenic to humans*";
(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 at the point of contact (e.g., hyperplasia).

As a clear majority of Panel 1 members recommended no cancer value is required for these three acrylates (Kirman et al., 2023), the need for deriving NSRL values for these chemicals is subject to debate. However in consideration of individuals whose conclusions differ significantly from the majority of expert panel as well as those for agencies who adopt a precautionary position as a matter of policy, NSRL values may be useful to some. Deriving NSRL values consistent with the scientific conclusions of Panel 1 and the prescriptive methods encoded by California for NSRL derivation is challenging. Language in California's Article 7 appears to offer some room for flexibility to permit the use of the best available science: "*Nothing in this article shall preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure to a listed chemical poses no significant risk.*" (ibid). With the spirit of this language in mind, the goal of this work is to extend and apply the work of Panel 1 to the process of deriving NSRL values for the three lower acrylates based upon a consideration of the mode of action (MOA), best available science, data, and risk assessment approaches. The methods and results of this expert panel engagement (Panel 2) are described below.

2. Methods and materials

2.1. Panel engagement

An expert panel was recruited, selected, and engaged utilizing the methods described in Kirman et al. (2019) as modified in Appendix A. Roles were defined for the review sponsor, review manager (SciPinion; authors CRK, SMH), and independent expert panel members. As noted above, the work of this panel builds upon the input received from a previous expert panel (Panel 1) that focused on the cancer WOE and MOA for the three acrylates (results reported in Kirman et al., 2023). For the sake of continuity, five panel members from Panel 1 were retained and two new members with expertise in benchmark dose (BMD) and statistics needed for NSRL calculations were added for this panel review. Multiple design elements were included in this review to minimize potential sources of bias and groupthink, and to improve transparency of the review (Appendix A), including these: (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) individual responses and comments from the panelists were recorded and are provided in their entirety (Appendix C) to ensure transparency, and minimize potential reporting bias; and (5) although individual responses are provided in this appendix, they are attributed to panelist's anonymous display names (e.g., to Expert 1, Expert 2, etc.) in order assure candid sharing of scientific opinion(s) on areas of controversy with minimal concern of potential adverse within-panel or external professional perceptions.

Review material (Appendix B) and charge questions (Appendix C) were defined by the review manager to include the results from Panel 1, as well as access to underlying cancer bioassays and supporting material for the selected acrylates for the panel to consult as needed. Interim results (e.g., strawman NSRL calculations) were included in the review material at the beginning of the later rounds to support the panel deliberations and answering the charge questions. After each round, charge question options that received support from a majority of the panel were carried forward for subsequent rounds; consideration of options with a minority support are described in the discussion section of this paper. Panelists were also given the opportunity to request access to additional publications/reports to support their assessment as needed.

2.2. Calculations

Based on input from Panel 1, which recommended a nonlinear approach using cancer precursor lesions, NSRL values were derived based on Panel 2 input using the following equation:

$$NSRL = POD_{HEC} / UF_{net} \quad \text{Eq.1}$$

where,

- POD_{HEC} = POD human equivalent concentration/dose calculated for inhalation and dermal studies as described below.
- UF_{net} = Net uncertainty factor, calculated as the product of individual uncertainty factors for interspecies variation (UFa), intraspecies variation (UFh), LOAEL-to-NOAEL extrapolation (UFl), subchronic-to-chronic extrapolation (UFs), and databased uncertainty (UFd), as defined by the panel.

For NSRL calculations based on inhalation studies (MA and EA), adjusted POD values were calculated based on panel input using USEPA's regional gas dose ratio (RGDR) approach (USEPA, 1994):

$$POD_{HEC} = POD_{cont} \times RGDR \times BR \times CF \quad \text{Eq.2}$$

where,

- POD_{HEC} = Human equivalent concentration for the POD for continuous exposure
- PODcont = POD adjusted for discontinuous exposure [e.g., POD x (ET/24 h) x (EF/7 days)]
- POD = POD in terms of exposure units as tested
- ET = Exposure time (e.g., 6 h daily)
- EF = Exposure frequency (e.g., 5 days weekly)
- RGDR =Regional gas dose ratio for extrathoracic effects, calculated using default values for minute volumes (0.25 and 13.8 L/min for rats and humans, respectively) and extrathoracic surface areas (15 cm^2 and 200 cm^2 for rats and humans, respectively) to yield an RGDR value of 0.24 (USEPA, 1994).
- BR = Breathing rate (20 m^3/day)
- CF = Conversion factor (1000 μg/mg)

Alternative methods for interspecies extrapolation (e.g., uncertainty factor application) and allometric scaling of dose as a power of body weight were also considered (Appendix B) and included in the discussion section.

For NSRL calculations based on dermal studies (2EHA), adjusted POD values were derived based on panel input using the following equation:

$$POD_{HED} = POD/100 \text{ x } EF/7 \text{ days x } V \text{ x } D \text{ x } CF/\ BW \quad \text{Eq.3}$$

Where,

- POD_{HED} = Human equivalent dose (mg/kg-day) for the POD for continuous exposure
- POD = Point of departure expressed in units as tested (% solution);
- EF = Exposure frequency, 3 days/week (Wenzel-Hartung et al., 1989);
- V = Volume of test solution applied to skin per day (0.025 mL/d; Wenzel-Hartung et al., 1989);
- D = Density of 2EHA (0.885 g/mL)
- CF = Conversion factor (1000 mg/g)
- BW = Mouse body weight (0.037 kg)

No additional adjustments were made to the applied dermal dose values to account for potential species differences in dermal absorption (mouse vs. human skin).

All BMD modeling was performed using USEPA's Benchmark Dose Software (BMDS version 3.3.2). Decisions for model selection, benchmark response rates, POD confidence limits were determined based on input from the panel. All summary statistics, calculations, and figures were prepared using Microsoft Excel (version 15.67).

3. Results

Results for Panel 2 are summarized and discussed below. The assessment focuses on decision options that received support from a majority of the panelists. Consideration of alternative decision options and minority positions is provided in the discussion section (Section 4).

3.1. Panel composition

The panel consisted of seven scientists with expertise in dose-response assessment, benchmark dose methods, and toxicity value derivation. Demographics, affiliations, and expertise metrics (e.g., means ± standard deviations) for this panel are as follows:

- •Advanced degrees: PhD (7)
- •Mean years of experience: 35 ± 16 years
- •Mean number of publications: 130 ± 85
- •Country of residence: Canada (1), Netherlands (1), United States (5)
- •Current sector of employment: Academia (2), Consulting (2), Retired/Government (1), Retired/Industry (1), Retired/Consulting (1)

3.2. Endpoint/data set selection

Historically, NSRL values derived by the State of California have been based on cancer endpoints. Point of contact tumors, including nasal tumors following inhalation exposure (JBRC, 2017b), 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. Proctor et al. (2018) concluded that EA-induced forestomach tumors are of limited human relevance due to lack of a tissue counterpart. Wibbertmann et al. (2021) concluded that MA-induced nasal tumors are of questionable relevance to human health risk assessment due to occurrence only at exposures exceeding a maximum tolerable concentration. Elmets and Yusuf (2020) also concluded that the skin tumors observed in C3H/Hej mice exposed to 2EHA were of questionable relevance to human cancer risk in that this strain exhibits dysregulated immune and inflammatory pathways. Lastly, multiple studies have also reported no increase in tumors at the point of contact following chronic exposures to acrylates (JBRC, 2017a; Reininghaus et al., 1991; Miller et al., 1985; Mellert et al., 1994).

Some studies have reported weak increases in the incidence in systemic tumors. These tumors sites include soft tissue sarcomas (combined across tissues), and combined hematopoietic/lymphoid cancers, pituitary adenoma, adrenal pheochromocytoma, and thyroid follicular cell adenoma (JBRC, 2017a,b; Reininghaus et al., 1991; Miller et al., 1985). The reports for 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 (e.g., thyroid tumors in animals exposed to EA; Rosol and Witorsch, 2021). Furthermore, due to the rapid and extensive carboxylesterase metabolism of acrylates to their common non-genotoxic and non-tumorigenic metabolite, acrylate (as reviewed in Johannsen et al., 2008; Suh et al., 2018), appreciable systemic doses of the highly protein- and thiol-reactive parent chemicals are not expected to arise that could result in systemic tumor formation.

It is for these reasons, as well as the general absence of a direct genotoxic response to serve as a tumor initiating event, that most of the panel (5/7) did not recommend the use of tumor incidence data as the basis for human health risk assessment for these three acrylates. Instead, strong preference was given to relying on non-neoplastic lesions (e.g., hyperplasia) as the bases for NSRL values. Epithelial hyperplasia, resulting from glutathione depletion and associated protein binding and cytotoxicity, was identified as a critical initiating event in the production of forestomach tumors in animals exposed to EA (Proctor et al., 2018).

Several non-neoplastic lesions observed at the point of contact during repeat-exposure toxicity studies received support from a majority of the panelists as the bases for NSRL calculations (Table 1). These effects were viewed by the panelists as critical precursor events to tumors observed at the point of contact in exposed animals, and include nasal and respiratory tract lesions in rats and mice exposed to MA or EA via inhalation (Wibbertmann et al., 2021 ; Reininghaus et al., 1991; JBRC, 2017b; Miller et al., 1985), and skin lesions in mice dermally exposed to 2EHA (Mellert et al., 1994; Wenzel-Hartung et al., 1989).

Endpoints receiving support from a minority of the panelists for MA include non-neoplastic lesions in the respiratory tract of male and female mice exposed via inhalation (JRBC, 2017), as well as no-effect levels for tumors in both sexes for the same study (Appendix C). Endpoints receiving support from a minority of the panelists for EA include no effect levels for tumors in female rats (Miller et al., 1985), as well as non-neoplastic forestomach lesions in male and female mice, and in male and female rats exposed via oral gavage (NTP, 1986). For 2EHA, a no effect level for skin tumors in male mice (Mellert et al., 1994) received support from a minority of panelists.

3.3. Dose-response assessment approach

Dose-response assessments include multiple decision points, including the following: endpoint/data set selection; dose measure selection (e.g., approach for calculating interspecies dose adjustments to determine human equivalent exposures; dose-response modeling decisions (best model selection; benchmark response rate, BMD confidence limits); and low-dose extrapolation (e.g., uncertainty factor selection). A summary of the best supported options for each of these decision points along with the rationales from the panel is summarized in Table 2.

3.4. Candidate point of departure values

Based upon the endpoints defined above, POD values (NOAEL, LOAEL, and or BMD values) were determined, expressed in terms of unadjusted exposure units as tested (Fig. 1). For MA, respiratory metaplasia of olfactory epithelium in rats was selected as the basis for NSRL calculation based on panel recommendations, yielding a point of departure of 18 ppm (11–27 ppm) (Table 3). For EA, non-neoplastic

Table 1
Candidate endpoints for supporting NSRL values (Q1.1-Q1.3 in Appendix C).

Acrylate	Panel Selection Frequency: Endpoint/Data set[a]	Rationale[b]
Methyl Acrylate	5 of 7: Non-neoplastic lesions in the nasal cavity of male rats exposed via inhalation over 2 years (See Wibbertmann et al., 2021 Supplemental Table 3; BASF AG, 1985; Hartwig and MAK Commission, 2019; Reininghaus et al., 1991) 4 of 7: Non-neoplastic lesions in the nasal cavity of female rats exposed via inhalation over 2 years (See Wibbertmann et al., 2021 Supplemental Table 3; BASF AG, 1985; Hartwig and MAK Commission, 2019; Reininghaus et al., 1991)	• This was identified as a well-conducted, good quality study, that relied upon chronic exposures to multiple treatment groups • This study also provides information on concentration x time that are important to understanding MOA
	5 of 7: Non-neoplastic lesions in the respiratory tract of male rats exposed via inhalation over 2 years (See Wibbertmann et al., 2021 Supplemental Table 6; JBRC, 2017b) 4 of 7: Non-neoplastic lesions in the respiratory tract of female rats exposed via inhalation over 2 years (See Wibbertmann et al., 2021 Supplemental Table 6; JBRC, 2017b)	• This was identified as a well-conducted, good quality study, that relied upon chronic exposures to multiple treatment groups • This study demonstrates a concentration-related increases in nasal tumors and non-neoplastic precursor lesions • Negative results in a companion mouse study, which was limited due to poor health and survival rates, make this a conservative choice
Ethyl Acrylate	5 of 7: Non-neoplastic olfactory lesions in male mice (Miller et al., 1985) 4 of 7: Non-neoplastic olfactory lesions in male rats (Miller et al., 1985)	• This study, which utilized multiple treatment groups and a chronic exposure duration, is considered to be of sufficient quality to support the derivation of a POD • Although nasal and forestomach tissues both show evidence of irritation following inhalation and oral exposures, respectively, the nasal lesions are considered to be more relevant to human health • Incidence and severity of the responses were generally greater in males compared to females, particularly at the lowest test concentration, and therefore are expected to provide a more conservative POD value
2-Ethylhexyl Acrylate	4 of 7: Non-neoplastic skin lesions in male mice (Mellert et al., 1994)	• Database for 2EHA is limited to dermal studies • This study utilized chronic exposure using three test concentrations (21.5–85% solutions), and as such may support dose-response assessment with some caveats (e.g., dermal studies are not typically used to derive toxicity values for risk assessment purposes)
	4 of 7: Non-neoplastic skin lesions in male mice (Wenzel-Hartung et al., 1989)	• Database for 2EHA is limited to dermal studies • This study provided exposure response data for chronic dermal exposure to three test concentrations (2.5–86.5% solutions), and as such may support dose-response assessment with some caveats (e.g., dermal studies are not typically used to derive toxicity values for risk assessment purposes)

[a] Only endpoint/datasets receiving an endorsement from a majority of panelists (4 or more) were carried through NSRL calculations in this paper. Endpoint/data sets receiving endorsement from a minority of the panel (see Appendix C) are considered in the discussion section.
[b] Non-neoplastic lesions were identified as the preferred bases for the NSRL values due to mechanistic reasons and limitations in available tumor data sets (see text).

olfactory lesions in male rats (Miller et al., 1985) were selected as the basis for NSRL calculation based on panel recommendations, yielding a point of departure of 18 ppm (8.0–19 ppm) (Table 4). To use the data set in BMD modeling (as requested by a panelist), the high test concentration (225 ppm) was dropped (exceeded maximum tolerated concentration), and the test concentration of 5 ppm from the follow-up study reported in this paper was included. For 2EHA, skin hyperplasia in male mice (Wenzel-Hartung et al., 1989) was selected as the basis for NSRL calculation based on panel recommendations, yielding a point of departure of 6.4% (4.9–10%) (Table 5). Alternative POD values based on other endpoints and/or response measures (e.g., NOAEL, LOAEL) are also included in Tables 3–5

3.5. Interspecies dose adjustments

Although clear consensus was not obtained for a preferred method for extrapolating POD values across species (e.g., allometric scaling of dose, RGDR approach, uncertainty factors), a decision was made to make the RGDR extrapolation the primary method since: (1) it reflects the best available science in that it is intended specifically for endpoints at the point of contact, whereas allometric scaling of dose is best applied to extrapolate the systemic dose of the parent chemical across species; and (2) it results in slightly lower (i.e., more conservative) values when compared to the other approaches. There were several panelists who suggested presenting all three recommended approaches for interspecies adjustments, and for this reason all are included in Appendix B and are discussed in Section 4 below.

3.6. Low-dose extrapolation/uncertainty factors

Input received from the panel during Round 1 of the review (abstract questions on uncertainty factor values without specific reference to endpoints or interspecies adjustments) yielded net uncertainty factors that ranged from 10 to 1000, with 100–300 considered to be representative of central tendency values based on panel input. Based upon the panel input, a net uncertainty factor of 100 was adopted for all three acrylates to account for interspecies and intraspecies variation as well as for other potential sources of uncertainty. In subsequent rounds of the review, several panel members recommended reducing the uncertainty factors used in the calculations to 30 (based on considerations that species differences in toxicokinetic factors are addressed in the RGDR approach used, variation in systemic toxicokinetic factors may not contribute to effects at the point of contact). In contrast, one panel member recommended increasing the uncertainty factor for precautionary reasons. To accommodate these differences in opinions, the net uncertainty factor of 100 was retained and a plausible range of uncertainty factor values (30–300) was also included as part of the calculations (Table 6).

3.7. No-significant-risk-level values

After adjusting for discontinuous inhalation exposures and converting units, the rodent POD values for MA and EA correspond to continuous exposures of 11 mg/m^3 (6.7–17 mg/m^3) and 13 mg/m^3 (5.8–14 mg/m^3). These values were then adjusted for species differences (RGDR) approach to which the UF of 100 was applied, and corresponding NSRL intakes of 530 μg/day (330–800 μg/day) and 640 μg/day (280–670 μg/day) were calculated (Table 6). Similarly, the rodent POD of 6.4% (4.9–10%) for dermal exposures 2EHA corresponds to an NSRL intake of 1700 μg/day (1300–2700 μg/day). Confidence in these values is dependent upon the route of exposure to which they are applied. For MA and EA, high confidence (mean confidence rating of 3.6–4 out of a

Table 2
Panel recommendations for the dose-response approach for NSRL derivation.

Decision Point (Charge question in Appendix C)	Option Best Supported (Based on Panel Response Mode)[a]	Rationale
Key endpoint (Q1.1–1.3, Q3.1)	Tumor precursor (non-neoplastic) lesions (see Table 1)	This decision reflects a primary conclusion and recommendation from Panel 1 (Kirman et al., 2023), which concluded that tumors from these acrylates most likely reflect a non-genotoxic mode of action that involves increased cell replication by cytotoxicity (see text). Alternative endpoints are considered in the discussion section.
Dose adjustments for Point of Contact Endpoints (Q1.4)	For inhalation exposures (MA and EA), administered concentration, adjusted for discontinuous exposure, adjusted for species differences using USEPA's RGDR method For dermal exposures (2EHA), administered doses were adjusted for discontinuous exposure	Since no clear consensus was reached by the panelists in Round 1 of the panel engagement, multiple approaches to adjusting dose were considered in Appendix B. USEPA's RGDR approach providing the lowest (most health protective) values for inhalation exposures to MA and EA, and was consistent with effects occurring at the point of contact. Alternative approaches for MA and EA are considered in the discussion section. No alternative approaches were suggested for adjusting the dermal doses for 2EHA.
Dose-response characterization (Q1.6)	Benchmark dose methods	When the data are sufficient, benchmark dose methods were strongly preferred over reliance upon NOAEL or LOAEL values for the POD
Benchmark Response Rate (Q1.7)	10%	This value generally serves as a default for the application of benchmark dose methods to endpoints considered, and will generally fall at the low end of the range of observation defined by the data sets. Alternative values (e.g., 5%) are considered in the discussion section.
BMD Confidence Limits (Q1.8)	Present lower confidence limit (LCL), maximum likelihood estimate (MLE), and upper confidence limit (UCL)	Providing all three values provides a more complete characterization of model uncertainty, than would be provided by just relying upon the LCL. Ratios of these values (e.g., BMD:BMDL) can serve as useful indicators of model reliability.
Dose-response model selection (Q1.9)	Based on goodness of fit measures (AIC, p-value)	There was general support for considering multiple models (rather than simply rely on the multistage model), with final model selection based on goodness of fit and visual inspection.
Low-Dose Extrapolation (Q1.10, Q3.1)	Nonlinear extrapolation (e.g., application of uncertainty factors)	Support for nonlinear extrapolation (uncertainty factor application/margin of exposure) is consistent with the conclusions and recommendations of Panel 1 (Kirman et al., 2023), which concluded that tumors from these acrylates most likely reflect a non-genotoxic mode of action that involves increased cell replication by cytotoxicity. Alternative extrapolation methods (e.g., linear) are considered in the discussion section.

[a] Explanatory text for panelists who selected "Other/It depends" were also consulted to establish the preferred option for each decision point (see)Appendix C.

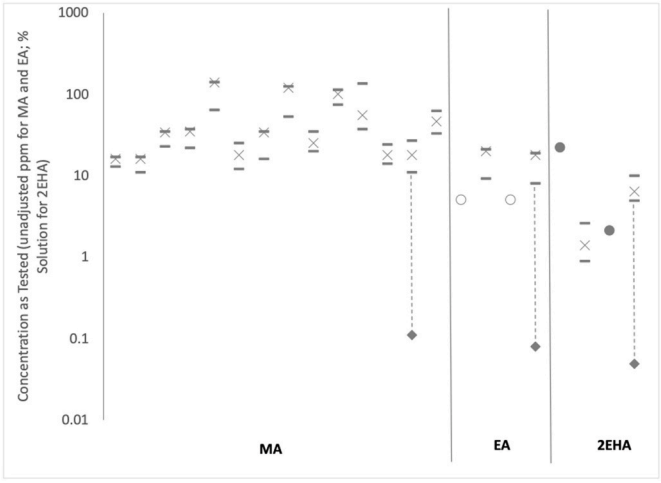

Fig. 1. POD values for MA, EA, and 2EHA (see Tables 3–5). X's = BMD10, bars = BMDL10, BMDU10; hollow circles = NOAEL; solid circles = LOAEL; dashed lines = uncertainty factor application; diamonds = value used to calculate NSRL.

maximum of 5) is assigned to the NSRL values when applied to address inhalation exposures, but confidence drops to low (mean confidence rating of 1.3–1.4) when applied to other routes, due to uncertainties associated with route-to-route extrapolation for point of contact effects (Table 6). For 2EHA, medium confidence (mean confidence rating of 2.6) is assigned to the NSRL value when applied to address dermal exposures, due to limitations in the dermal bioassays, as well as the uncertainties associated with adjusting the applied doses to calculate an NSRL. The panel does not recommend applying this NSRL value to other routes of exposure (mean confidence rating of 0.6). These confidence ratings are consistent with a majority of the panel who indicated that the NSRL values derived here based on point-of-contact effects should only be applied to the route of exposure tested.

4. Discussion and conclusions

An expert panel was engaged to guide the derivation of NSRL values for three lower acrylates, MA, EA, and 2EHA, based on best available science. Input from the panel resulted in NSRL values of 530 μg/day (330–800 μg/day), 640 μg/day (280–670 μg/day), and 1700 μg/day (1300–2700 μg/day) for MA, EA, and 2EHA, respectively. These values are best applied (i.e., with medium to high confidence) to the exposure routes used in the underlying toxicity studies (inhalation for MA and EA; dermal for 2EHA), and confidence in these values is considerably lower if they are applied to other routes of exposure due to the uncertainties associated with route-to-route extrapolation of effects observed at the point of contact. These values reflect input from the expert panel for key decisions in the dose-response assessments.

The potential impact of alternative options for these decision points on the resulting NSRL values, including options that reflect positions from a minority of the panel, are discussed below.

- *Alternative Endpoints/Data Sets* – Many endpoints/data sets were considered by the panel (Tables 3–5; Appendix C). Alternative endpoints/data sets for MA (i.e., other precursor lesions or tumor endpoints), including those receiving a minority of support from the panel, can be used to calculate POD values that are up to an order of magnitude higher or lower than the final POD values selected. Similarly, alternative endpoints/data sets for EA and 2EHA, including those receiving a minority of support from the panel, can be used to calculate POD values that are approximately equivalent to

Table 3
Candidate POD values for methyl acrylate based on data sets/endpoints.

Data set/Endpoint	Subset/Note	Type	Best Fitting BMD Model			POD MLE, ppm unadjusted (LCL-UCL)
			Model	P-Value	AIC	
Non-neoplastic lesions in the nasal cavity of male rats exposed via inhalation over 2 years (See Wibbertmann et al., 2021 Supplemental Table 3; BASF AG, 1985; Hartwig and MAK Commission, 2019; Reininghaus et al., 1991)	All durations	BMD10	multistage-3	0.801	72	16 (13–17)
	24-months only	BMD10	multistage-3	0.998	58	16 (11–17)
Non-neoplastic lesions in the nasal cavity of female rats exposed via inhalation over 2 years (See Wibbertmann et al., 2021 Supplemental Table 3; BASF AG, 1985; Hartwig and MAK Commission, 2019; Reininghaus et al., 1991)	All durations	BMD10	logistic	1	27	34 (23–35)
	24-months only	BMD10	logistic	1	34	35 (22–37)
Non-neoplastic lesions in the respiratory tract of male rats exposed via inhalation over 2 years (See Wibbertmann et al., 2021 Supplemental Table 6; JBRC, 2017b)	Adhesion: turbinate	BMD10	weibull	1	55	138 (64–140)
	Atrophy: olfactory epithelium	BMD10	dichotomous Hill	0.882	26	18 (12–25)
	Basal cell hyperplasia: olfactory epithelium; drop high concentration	BMD10	weibull	1	52	34 (16–35)
	Degeneration: gland	BMD10	log-logistic	1	19	119 (53–125)
	Goblet cell hyperplasia	BMD10	probit	0.705	92	25 (20–35)
	Hyperplasia: transitional epithelium	BMD10	multistage-3	0.986	66	100 (74–114)
	Inflammation: olfactory epithelium	BMD10	weibull	1	79	55 (37–136)
	Inflammation: respiratory epithelium	BMD10	logistic	0.994	246	18 (14–24)
	Respiratory metaplasia: olfactory epithelium	BMD10	log-logistic	0.893	150	18 (11[a]-27)
	Squamous cell metaplasia: respiratory epithelium	BMD10	multistage-3	0.972	74	46 (33–62)

[a] Value was selected to serve as the basis for the NSRL calculations for MA.

Table 4
Candidate POD values for ethyl acrylate based on data sets/endpoints.

Data set/Endpoint	Subset/Note	POD Type	Best Fitting BMD Model			POD, ppm unadjusted (LCL-UCL)
			Model	P-Value	AIC	
Non-neoplastic olfactory lesions in male mice (Miller et al., 1985)	BMD modeling not performed since incidence at lowest test concentration ≫10% response rate in the primary study; follow-up study using 5 ppm yielded no changes in nasal tissue	NOAEL	NA	NA	NA	5 (NA)
	High concentration group dropped (>MTC); 5 ppm group included	BMD10	Dichotomous Hill	NA	268	20 (9.2–21)
Non-neoplastic olfactory lesions in male rats (Miller et al., 1985)	BMD modeling not performed since incidence at lowest test concentration ≫10% response rate in the primary study; follow-up study using 5 ppm yielded no changes in nasal tissue	NOAEL	NA	NA	NA	5 (NA)
	High concentration group dropped (>MTC); 5 ppm group in follow-up study included	BMD10	Dichotomous Hill	NA	184	18 (8.0[a]-19)

[a] Value was selected to serve as the basis for the NSRL calculations for EA.

Table 5
Candidate POD values for 2-EthylHexyl acrylate based on data sets/endpoints.

Data set/Endpoint	Subset/Note	Type	Best Fitting BMD Model			POD, % Solution Applied unadjusted (LCL-UCL)
			Model	P-Value	AIC	
Non-neoplastic skin lesions in male mice (Mellert et al., 1994)	BMD modeling not performed since incidence at lowest test concentration ≫10% response rate	LOAEL	NA	NA	NA	22 (NA)
	Hyperplasia; BMDL of 0.89% is more than 20x below lowest test concentration of 21.5% (i.e., well outside the range of observation) and therefore is not recommend	BMD10	Log-logistic	0.389	158	1.4 (0.89–2.6)
Non-neoplastic skin lesions in male mice (Wenzel-Hartung et al., 1989)	BMD modeling not performed since incidence for some endpoints (thickened) at lowest test concentration ≫10% response rate	LOAEL (for all dermal effects)	NA	NA	NA	2.1 (NA)
	Hyperplasia	BMD10	Multistage-3	0.447	219.2	6.4 (4.9[a]-10)

[a] Value was selected to serve as the basis for the NSRL calculations for 2EHA

Table 6
NSRL values for ThreeLower acrylates.

Chemical	Endpoint Sex, Species Route (reference)	Rodent POD[a]		NSRL Calculation		Confidence in NSRL (mean rating on 1–5 scale, 5 = highest)[c]
		Concentration (units as tested)	Continuous Exposure, POD value (mg/m^3)	UF Value (plausible range of UF values)[b]	NSRL value, ug/day (values based on plausible range of UF values)	
Methyl Acrylate	Olfactory epithelium metaplasia Male rats Inhalation	BMDL10 = 11 ppm BMD10 = 18 ppm BMDU10 = 27 ppm	6.7 11 17	100 (30–300)	330 (110–990) 530 (180–1600) 800 (270–2400)	High (4.0)/Low (1.4)
Ethyl Acrylate	Non-neoplastic olfactory lesions Male rats Inhalation (Miller et al., 1985; drop high test group, and add 5 ppm test group)	BMDL10 = 8.0 ppm BMD10 = 18 ppm BMDU10 = 19 ppm	5.8 13 14	100 (30–300)	280 (93–840) 640 (210–1900) 670 (220–2000)	High (3.6)/Low (1.3)
2-Ethylhexyl Acrylate	Skin hyperplasia Male mice Dermal (Wenzel-Hartung et al., 1989)	BMDL10 = 4.9% BMD10 = 6.4% BMDU10 = 10%	NA	100 (30–300)	1300 (440–4000) 1700 (580–5200) 2700 (910–8200)	Medium (2.6)/Not recommended (0.6)

NA = not applicable.
[a] POD values from Table 3 (MA), Table 4 (EA), and Table 5 (2EHA).
[b] Changes in UF values result in reciprocal changes to the NSRL values calculated.
[c] Confidence (mean score out of 5) if NSRL is applied to the route as tested/confidence (mean score out of 5) if NSRL is applied to other routes of exposure; n = 7. High: mean score>3.33; Medium: 3.33 > mean score>1.67; Low: mean score<1.67.

or up to an order of magnitude higher than the final selected POD values.

- *Alternative Points of Departure* – Although a majority of the panelists recommended the use of a 10% benchmark response rate, which generally serves as a default value for risk assessment purposes in the U.S., one panelist recommended the use of a 5% benchmark response rate. A 5% response rate is sometimes used for specific endpoints within the U.S. (e.g., developmental effects), and also serves as default value used by other agencies/countries as a matter of policy (e.g., Health Canada). For most data sets, the BMD05 values were approximately 2-fold lower than their corresponding BMD10 values. For EA, consideration was also given to using the NOAEL value of 5 ppm as the POD from the follow-up study (rather than concurrent treatment group) reported in the same publication (Miller et al., 1985), which is slightly lower than the selected BMDL10 value of 8 ppm. Similarly, for 2EHA consideration was also given to using the LOAEL value of 2.1% as the POD for all mouse dermal effects (e.g., subcutis skin thickening; Wenzel-Hartung et al., 1989) which is approximately 2.5-fold lower than the selected BMDL10 value of 4.9% for mouse skin hyperplasia.
- *Alternative Dose-Response Models* – All dichotomous models available in USEPA's BMDS program were considered (Appendix D). For MA, alternative dose-response models applied to the key data set yielded POD values that were up to 2-fold lower or higher than yielded from the best fitting model (log-logistic). For EA, alternative dose-response models applied to the key data set yielded POD values that were up to 7-fold lower than yielded from the best fitting model (dichotomous hill). For 2EHA, alternative dose-response models applied to the key data set yielded POD values that were up to 3-fold higher than yielded from the best fitting model (multistage model).
- *Alternative Interspecies Dose Adjustments* – Two alternative methods for adjusting doses across species were considered (allometric scaling, application of an uncertainty factor of 3 for species differences in toxicokinetics) and received support from some panel members. These alternative approaches resulted in NSRL values that were slightly higher (up to ~2-fold) than the values calculated using the RGDR approach (Appendix B). For 2EHA, no adjustments were made to account for differences across species in dermal absorption. Due to differences in skin thickness (mouse < human), this approach is expected to be conservative.
- *Alternative Uncertainty Factor Values* – A net uncertainty factor of 100 was used to calculate the NSRL values for MA, EA, and 2EHA. Because there was discussion amongst the panel about lowering and/or increasing the uncertainty factor, a plausible range of uncertainty factors (30–300) was also included (Table 6).
- *Alternative NSRL Approach* – A minority of the panelists maintained that Article 7 requires that the NSRL value be derived using tumor response data (rather than precursor lesions), allometric scaling of dose (rather than RGDR methods), multistage model (rather than best fitting model), and low-dose linear assumption for determining 1×10^{-5} risk (rather than application of uncertainty factors). Application of these methods would result in alternative NSRL values that are approximately 3- to 30-fold lower than calculated here for the three lower acrylates. However most panelists felt that the default methods described by Article 7 do not reflect the best available science for these chemicals. In fact, the majority of Panel 1 was of the opinion that these structurally related chemicals are unlikely to pose a cancer risk to human populations and that derivation of NSRL values was not necessary.

This last point highlights the challenge associated with deriving NSRL values under California Code of Regulations (Title 27, Article 7) for chemicals that cause tumors via a nongenotoxic mode of action. A clear majority of the panel indicated that Article 7 has not kept pace with science and is in need of an update. This regulation could be improved with the inclusion of language that places emphasis on data, mode of action, weight of evidence, and toxicological judgement. This change would provide greater flexibility in determining what exposure levels constitutes a "significant" risk. The challenge is exacerbated by the encoding of NSRL methods into regulation, rather than guidelines that can be updated as needed to keep pace with developing science. This assessment for three lower acrylates serves as a case study for deriving NSRL values for nongenotoxic chemicals in a manner that reflects a mode of action understanding and an appropriate dose response approach, while still using conservative methods protective of health for determining levels of exposure that pose no significant risk.

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CRediT authorship contribution statement

C.R. Kirman: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **P.J. Boogaard:** Writing – review & editing. **J.S. Bus:** Writing – review & editing. **V.L. Dellarco:** Writing – review & editing. **K. Shao:** Writing – review & editing. **B.R. Stern:** Writing – review & editing. **S.M. Hays:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors, CRK and SMH are owners of SciPinion and, thus, have a financial interest in the content of this manuscript.

Data availability

data provided in supplemental material

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Appendix A. Supplementary data

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