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Application of a unified probabilistic framework to the dose-response assessment of acrolein

Todd Blessinger[a,*], **Allen Davis**[a], **Weihsueh A. Chiu**[b], **John Stanek**[c], **George M. Woodall**[c], **Jeff Gift**[c], **Kristina A. Thayer**[c], **David Bussard**[d]

[a]Center for Public Health and Environmental Assessment (CPHEA), United States Environmental Protection Agency (US EPA), Mail code 8623R, 1200 Pennsylvania Ave NW, Washington, DC 20460, USA

[b]Department of Veterinary Integrative Biosciences, 4458 TAMU, Texas A&M University, College Station, TX 77843-4458, USA

[c]CPHEA, 109 T.W. Alexander Drive, US EPA, Mail code B243-01, Research Triangle Park, NC 27711, USA

[d]Office of the Science Advisor, Policy and Engagement, US EPA, 1300 Pennsylvania Ave NW, Mail code 8104R, Washington, DC 20460, USA

Abstract

Background: In quantitative chemical risk assessment, a reference value is an estimate of an exposure to a chemical that is "likely to be without appreciable risk." Because current "deterministic" approaches do not quantitatively characterize the likelihood or severity of harm, the National Academies has recommended using reference values derived from a risk-specific dose that are treated as random variables, with probability distributions characterizing uncertainty and variability.

Objectives: In order to build familiarity and address issues needed for routine and standardized derivation of probabilistic risk-specific dose distributions, a case example applying the unified probabilistic framework presented in Chiu and Slob (2015) is developed for acrolein. This case study is based on an updated systematic evidence map of literature (Keshava et al., 2020) identifying nasal lesions reported in Dorman et al. (2008) as the most appropriate endpoint and study for reference value derivation.

[*]Corresponding author. blessinger.todd@epa.gov (T. Blessinger).

CRediT authorship contribution statement

Todd Blessinger: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Project administration, Supervision. **Allen Davis:** Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Weihsueh A. Chiu:** Conceptualization, Writing - original draft, Writing - review & editing. **John Stanek:** Writing - original draft, Writing - review & editing. **George M. Woodall:** Writing - review & editing, Visualization, Writing - original draft. **Jeff Gift:** Writing - review & editing. **Kristina A. Thayer:** Conceptualization, Writing - review & editing, Writing - original draft. **David Bussard:** Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Methods: The probability distribution was calculated for the risk-specific dose, which in this implementation of the approach was calculated for the dose at which 1% of the human population is estimated to experience minimal lesions, and a probabilistic reference value was computed as the 5th percentile of this distribution. A deterministic reference value was also derived for comparison, and a sensitivity analysis of the probabilistic reference value was conducted investigating alternative assumptions for the point of departure type and exposure duration.

Results: The probabilistic reference value of 6×10^{-4} mg/m^3 was slightly lower than the deterministic reference value of 8×10^{-4} mg/m^3, and the risk-specific dose distribution had an uncertainty spanning a factor of 137 (95th-5th percentile ratio). Sensitivity analysis yielded slightly higher probabilistic reference values ranging between 9×10^{-4} mg/m^3 and 2×10^{-3} mg/m^3.

Conclusions: Using a probabilistic approach for deriving a reference value allows quantitative characterization of the severity, incidence, and uncertainty of effects at a given dose. The results can be used to inform risk management decisions and improve risk communication.

Keywords

Risk assessment; Quantitative uncertainty analysis; Approximate probabilistic analysis; Dose-response; Reference dose; Reference concentration

1. Introduction

In quantitative risk assessment of chemical toxicity, a reference value represents “an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime” (U.S. EPA, 2002). Currently, the reference value is calculated from a point of departure (POD) based on evaluation of the available hazard and dose-response data. If the toxicity data are amenable to dose-response modeling, the Benchmark Dose (BMD) can be estimated and its statistical lower bound, the BMDL, used as the preferred POD. If available data are not appropriate for dose-response modeling, the POD may be a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL). In cases where multiple endpoints are analyzed for dose-response, multiple ‘candidate’ PODs may be developed. To account for limitations in available data, the calculated POD is then typically divided by a series of uncertainty factors (UFs) that can take on one of a finite set of values (commonly 1, 3, or 10) to derive the reference value. In cases where sufficient chemical-specific data are available, data-derived extrapolation factors can be used instead of one of these “default” values (U.S. EPA, 2014).

The utility of this approach, defined here as a “deterministic” reference value, is limited in that it does not quantitatively characterize the likelihood of harm to an individual person at a given dose or the degree or severity of that harm. To address these limitations, a number of researchers and organizations have recommended using a “probabilistic” approach to derive a reference value (Hattis et al., 2002; Slob and Pieters, 1998; Baird et al., 1996; NRC, 1994). Most recently, the National Research Council (NRC, 2014, 2009) recommended using as the

basis for a reference value a “risk-specific” dose, which incorporates uncertainty and variability into its calculation, as a tool for risk characterization. In response, the World Health Organization/International Programme on Chemical Safety (IOMC ED, 2017) and Chiu and Slob (2015) developed a framework for calculating a “probabilistic reference value” using the concept of the HD_M^I, the human dose associated with magnitude M of an adverse effect and incidence I in the population. The HD_M^I is treated as a random variable with a probability distribution from which the probabilistic reference value is derived. In this framework, the probabilistic reference value can be represented as a value or set of values selected from a distribution that incorporates uncertainty and variability in a probabilistic manner. As such, it could be a central estimate, a confidence range, or a probabilistic lower bound. This probabilistic framework assists in enhancing transparency in determining the reference value by quantitatively representing the “appreciable risk” of experiencing an adverse effect through the magnitude M and how “likely” the effect is through the incidence I (to characterize variability) and use of a statistical confidence interval (to characterize uncertainty). Thus, defining the probability distribution of HD_M^I allows the estimation of the uncertainty in the reference value and risk-specific dose across a variable population.

Chiu et al. (2018) compared deterministic reference values and probabilistic reference values for a large number of chemicals and endpoints where the probabilistic reference value was defined as the 95% lower confidence bound of the HD_M^I distribution for I = 1%. For most of the 608 chemicals analyzed, the two values differed by less than an order of magnitude. However, this analysis focused only on oral exposure, and additional application with specific examples is required to build familiarity and address issues that need to be considered for more routine and standardized implementation, e.g., guidance on selection of input parameters when empirical evidence is lacking. To this end, a case study was conducted on acrolein for comparison of a deterministic inhalation reference value (deterministic IRV) for chronic exposure to a probabilistic inhalation reference value (probabilistic IRV). Acrolein was selected in part because chronic health values have been developed by several entities, including Environmental Protection Agency’s Integrated Risk Information System (IRIS), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA), Texas Commission on Environmental Quality (TCEQ), National Institute for Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA). Thus, there is broad familiarity with the chemical and its database, which should help multiple health agencies evaluate the utility of moving toward probabilistic approaches. In addition, the two most recent assessments (TCEQ, 2016; OEHHA, 2008) relied on the same endpoint and study, lesions in the nasal epithelium (i.e., nasal lesions) in a study by Dorman et al. (2008) to derive a chronic inhalation toxicity value. A recent systematic evidence map confirmed Dorman et al. (2008) as still the most appropriate study for deriving a chronic inhalation reference value (Keshava et al., 2020).

For this study, a probabilistic IRV for nasal lesions was computed using the HD_M^I-based framework developed by WHO/IPCS, using default probability distributions for the HD_M^I components. This probabilistic IRV was compared to the deterministic IRV derived using the process recommended in the general guidelines for risk assessment put forth by the National Research Council (NRC, 1983) and EPA’s *Framework for Human Health Risk*

Assessment to Inform Decision Making (U.S. EPA, 2014). In addition, a sensitivity analysis was conducted in which selected non-default probability distributions were used for some of the HD_M^I components and the resulting probabilistic IRVs compared. Finally, the HD_M^I probability distribution is estimated for various selected values of human incidence I.

2. Methods

2.1. Derivation of deterministic inhalation reference value

The deterministic IRV was derived using the histopathology data obtained from Dorman et al. (2008) following the general guidelines for risk assessment (U.S. EPA, 2014; NRC, 1983). A systematic evidence map was conducted to confirm Dorman et al. (2008) as still the most suitable study for chronic toxicity value derivation (Keshava et al., 2020). To identify a POD from which to calculate the deterministic IRV, it is generally preferred to use a BMD approach (U.S. EPA, 2012a), which consists of fitting statistical models to the dose-response data and using the fit results to estimate the BMD that yields a pre-selected BMR. Under this approach, the benchmark dose lower limit (BMDL), a 95% lower confidence bound of the BMD, is typically used as the POD. However, the nasal lesion response observed in Dorman et al. (2008) increased from near-minimal to near-maximal response between two adjacent dose groups, a pattern that is often not recommended for the BMD approach by EPA guidance (U.S. EPA, 2012a); thus, a NOAEL-based method was instead used to identify the POD.

First, because the deterministic IRV is a value that assumes continuous human exposure over a lifetime, the POD was duration-adjusted to account for the non-continuous exposure regimen used in this study. The duration-adjusted POD for nasal lesions was then converted to a human equivalent concentration (POD_{HEC}) using an appropriate dosimetric adjustment factor (DAF). A DAF is a ratio of animal and human physiologic parameters that is dependent on the nature of the contaminant (i.e., particle or gas) and the target site (i.e., respiratory tract or remote to the portal-of-entry [i.e., systemic]). As outlined in (U.S. EPA, 1994; U.S. EPA, 2002; U.S. EPA, 2012b), dosimetry models and chemical- and species-specific parameters represent optimal approaches for dosimetry and interspecies extrapolation. For acrolein, advanced computational fluid dynamic modeling results (Corley et al., 2012; Schroeter et al., 2008) were evaluated and used as appropriate for calculation of the POD_{HEC} (Keshava et al., 2020). The deterministic IRV was then calculated by dividing the POD_{HEC} by the composite uncertainty factor (UF_C):

$$\text{deterministic} \quad \text{IRV} = \frac{\text{POD}_{\text{HEC}}}{\text{UF}_c}. \tag{1}$$

The UF_C is the composite uncertainty factor considering variations in sensitivity among humans (UF_H), differences in response due to exposure between animals and humans (UF_A), the duration of exposure in the key study compared to the lifetime of the species studied (UF_S), extrapolation from a LOAEL rather than a NOAEL (UF_L), and the completeness of the toxicology database (UF_D) (U.S. EPA, 2002).

2.2. Approximate probabilistic analysis

This analysis develops a probabilistic calculation of risk-specific doses, where the goal is to probabilistically incorporate adjustments and uncertainty when extrapolating dose-response results from animal data to the human population. To that end, as described in IOMC ED (2017) and Chiu and Slob (2015), the probabilistic risk-specific dose HD_M^I is defined as the human dose or exposure (HD) at which a selected fraction (or incidence), I, of the human population would show an effect of magnitude (or severity) M or greater for the critical effect considered. This quantity is represented by a random variable and can be calculated as

$$HD_M^I = \frac{POD}{AF_1 \times \cdots \times AF_k}, \quad (2)$$

where each AF_i represents an "adjustment factor" and k is the number of AFs. Every component in Eqn (2) is treated as a continuous random variable with a distribution reflecting uncertainty therein. Thus, HD_M^I is also a random variable with its own distribution. The value of incidence I can be fixed or varied depending on risk management considerations; different choices of I are reflected in different values of the AF for human variability (analogous to the traditional UF_H). The value of I is usually assigned a value that is sufficiently low, such as 1%, to protect most of the population from experiencing the adverse event at the value of M; it can be assigned lower values for more severe effects. Additionally, in some cases the value of magnitude M can also be allowed to vary.

The World Health Organization's International Programme of Chemical Safety (IPCS) (IOMC ED, 2017) released an Excel-based spreadsheet tool, the Approximate Probabilistic Analysis spreadsheet (APROBA), as a relatively accessible software tool for applying Eq. (2). Under APROBA, the HD_M^I components in Eq. (2) are treated as independent lognormally distributed random variables. By Eq. (2), HD_M^I is then also lognormally distributed, and a probabilistic description of the inhalation reference value can be provided, for example, as a selected set of percentiles (e.g., 5th and 95th percentiles, or the median, 50th percentile) of the HD_M^I distribution. In particular, a lower percentile (e.g., 5th percentile) can be used as the probabilistic IRV to provide a high degree of confidence (e.g., 95% confidence) that a lower value is not necessary to achieve the target incidence I. By default, APROBA incorporates the following HD_M^I components:

1. POD
2. Interspecies scaling AF
3. AF related to remaining interspecies toxicokinetic/toxicodynamic (TK/TD) aspects
4. Duration extrapolation AF
5. Intraspecies variability AF

Additional AFs can be included to account for other areas of adjustment or uncertainty, as long as they are assumed to be lognormal and independent of the other components. Because APROBA is estimating a confidence range and a probabilistic IRV associated with a specific

effect, it does not include an adjustment factor for extrapolating to more sensitive effects occurring at a given dose, analogous to the database UF for a deterministic reference value.

For the default components listed above, APROBA provides provisional lognormal parameter values (specifically, for the 50th percentile and ratio 95th percentile/50th percentile) that are derived from empirical data reviewed by IOMC ED (2017). These values are determined based on the following characteristics of the study and endpoint under consideration:

1. Type of endpoint: dichotomous or continuous
2. Type of POD: NOAEL or BMDL
3. Route of exposure: oral, inhalation, or dermal
4. Exposure duration: chronic, subchronic, subacute, or reproductive/developmental
5. Test species: rat or mouse

Regarding the POD type, if a BMDL is used, the POD distribution is determined from the dose-response modeling results, and the user must specify the parameters. If a NOAEL is used, the POD distribution is derived from empirical data.

For interpreting dichotomous endpoints, the IOMC ED (2017) framework has two options, referred to as “quantal-deterministic” and “quantal-stochastic.” Quantal-deterministic is used when there exists an underlying continuous endpoint with a cut-off above (or below) which the quantal endpoint is considered positive; an example is a histopathological endpoint which is gradually increasing in severity but is scored as quantal based on a severity-related cut-off. When using the quantal-deterministic option, the ED_{50} of the animal incidence data is used as the POD. Here, the ED_{50} (“effective dose 50”) represents the concentration at which the “typical” (or median) animal exhibits the effect [see discussion in IOMC ED (2017) and Chiu and Slob (2015)]. Only the center of the dose-response curve from the animal data is used because estimating lower percentiles would require using the variation in incidence across doses in the animal study, which is considered not sufficiently informative of human variation. Thus, for this option, M corresponds to the severity of the dichotomous endpoint (e.g., “minimal lesions”) for which the incidence data are analyzed, and is not allowed to vary.

The quantal-stochastic option is used for endpoints for which there is some basis to conclude the mechanism is stochastic with each individual in the study population having some risk of the effect; such endpoints include, for example, cancer effects and malformations. In the quantal-stochastic case, the observed incidence in the population reflects the average individual risk probability, and the value of M can be set to any risk value of interest. This value is generally determined by risk management considerations such as endpoint severity; it is typically set equal to the BMR from dose-response modeling when a BMDL is used as the POD.

For any HD_M^I component, the user can use parameter values other than the provisional ones. Also, if non-default AFs are included, the user must determine the appropriate parameter values and enter them manually. The APROBA spreadsheet and inputs were applied to the

critical effect for acrolein of increased nasal lesions in rats from Dorman et al. (2008). The inputs and resulting outputs for all analyses can be found at Blessinger (2020).

3. Results

3.1. Deterministic reference value

The POD used to derive the deterministic IRV was based upon the results of the Dorman et al. (2008) study, which identified a NOAEL of 0.2 ppm (0.46 mg/m^1) for nasal respiratory epithelium lesions in the F344 rat (Keshava et al., 2020). In particular, the derivation of the deterministic and probabilistic reference values are based on the incidence of nasal respiratory epithelial hyperplasia in level II of the lateral wall; as reported in Table 2 of Dorman et al. (2008) (see Section 3.2.2 below for a full discussion of the data). As discussed in Section 2.1, a benchmark dose approach was not used because the nasal lesion incidence data had a minimal-to-maximal dose-response pattern. Therefore, derivation of the deterministic IRV was based on the use of a NOAEL as the POD with application of uncertainty factors. The POD was first adjusted from the dosing regimen of 0.46 mg/m^3 for 6 hr/day, 5 days/week for 13 weeks to a continuous exposure of 0.082 mg/m^3.

For acrolein, the Computational Fluid Dynamic modeling results (Corley et al., 2012; Schroeter et al., 2008) could be considered for interspecies extrapolation and calculation of the POD_{HEC}. Both studies estimated flux in the nasal cavities of rats and humans at various acrolein exposure concentrations. In general, the modeling results indicate that where dosimetric comparisons can be made, flux estimates in the nasal regions for a given acrolein exposure concentration are greater in the rat than the human. However, because comparative flux estimates were not provided in rats and humans over a range of exposure concentrations or at the NOAEL of 0.2 ppm acrolein for nasal respiratory epithelium lesions, quantitative application of these results is limited. Therefore, a DAF of 1 for interspecies extrapolation could be considered appropriate (Keshava et al., 2020). Applying this value to the duration-adjusted POD value of 0.082 mg/m^3 yields a POD_{HEC} of 082 mg/m^3.

The value of UF_C was calculated as the product of five uncertainty factor values (Table 1), as outlined by the U.S. EPA Risk Assessment Forum (U.S. EPA, 1994; U.S. EPA, 2002). The UF for interspecies extrapolation (UF_A) comprises two areas of uncertainty: toxicokinetics and toxicodynamics. For acrolein, chemical-specific dosimetric modeling was used to calculate the HEC, as described in Keshava et al. (2020); thus, a UF_A of 3 was applied to account for remaining uncertainty in toxicodynamics (U.S. EPA, 1994; U.S. EPA, 2002). A full value of 10 was applied to account for interindividual differences in sensitivity in humans (UFH) given that no chemical-specific information is currently available to define a more appropriate value for this uncertainty factor. No UF_L was needed as the POD was based on a NOAEL. For the subchronic-to-chronic uncertainty factor (UF_S), a value of 3 ($10^{1/2}$) was applied to adjust from subchronic to chronic duration. At exposure concentrations and locations where lesions were observed, lesion incidence was maximal or near-maximal. In addition, lesion severity did not appear to increase with increasing duration of exposure. Furthermore, in the majority of cases, nasal lesions persisted two months after the end of acrolein exposures. However, lesion severity and the number of sections with lesions appeared to increase with increasing exposure concentration. Together, these

observations suggest that acrolein-induced nasal lesions are primarily dependent on exposure concentration. With few exceptions, nearly every animal had nasal lesions in the tissue sections evaluated at the end of the 13-week exposure period to the highest concentration tested. Two months following cessation of exposure, only partial recovery of nasal lesions was observed. These data reduce the likelihood that longer duration exposures would cause significant lesion progression, thus supporting a reduction in the UFs from 10 to 3.

As discussed in U.S. EPA (2003), a value of 1 was applied to the database uncertainty factor (UFD) because the database for acrolein was considered complete. The available inhalation database includes subchronic toxicity studies in multiple species, and a one-generation inhalation reproductive toxicity study of acrolein in Fisher 344 rats that revealed no reproductive or developmental effects. Acrolein's high reactivity at the point of contact and the evidence for minimal systemic distribution of acrolein obviates the need for additional studies of repeat-dose toxicity or reproductive/developmental toxicity.

The value of the UF_C was 100, the product of the UF values in Table 1. Therefore, the resulting value of the deterministic IRV was

$$\text{deterministic} \quad \text{IRV} = \frac{0.082 \text{mg/m}^3}{100} = 8.2 \times 10^{-4} \text{mg/m}^3 .$$

3.2. Approximate probabilistic analysis

3.2.1. Primary analysis results—To initiate the APROBA analysis, the characteristics of the Dorman et al. (2008) study and nasal lesion endpoint and the magnitude of effect M and human incidence I were entered into APROBA (Table 2) for determining the provisional lognormal parameter values of the components. Because nasal lesions are a histopathological endpoint, with the responses reported in Dorman et al. (2008) reflecting the fraction of animals graded with severity level ≥ 1 (at least "minimal"; see Keshava et al. (2020), for details), the quantal-deterministic option was used in APROBA. Thus, as discussed in Section 2.2, the ED_{50} is the desired POD, which represents the concentration at which the "typical" (or median) animal has lesions of severity level ≥ 1, or "minimal severity." For nasal lesions from Dorman et al. (2008), the magnitude of effect M is "minimal severity." The value 1% was selected as the incidence I to protect a large proportion (99%) of the population. Therefore, the APROBA analysis was used to estimate the distribution of $HD_{\text{minimal}}{}^{01}$, the concentration that results in lesions of at least minimal severity in the nasal respiratory epithelium in 1% of a general human population.

As indicated in Section 2.1, the NOAEL was used as the POD for the deterministic IRV because of the rapid increase in incidence of nasal lesions from Dorman et al. (2008) from no animals affected at the NOAEL to almost all animals affected at the LOAEL. However, when considering an estimate of the ED_{50}, rather than a lower percentile, the change in incidence from minimal response at the NOAEL to maximal response at the LOAEL provides strong constraints on the value of the ED50. That is, it is highly likely that the ED50 is between the NOAEL and LOAEL. Therefore, the NOAEL (0.082 mg/m^3) and

LOAEL (0.246 mg/m^3) were treated as the LCL and UCL, respectively, of the POD distribution for the ED_{50}, thereby implying that the interval from the NOAEL to the LOAEL provides 90% coverage of the ED50. To accomplish this in APROBA, “BMDL” was entered as the POD type, rather than “NOAEL”, because the confidence limits were determined from the dose-response data, not from empirical data; the NOAEL and LOAEL values were entered as the BMDL and BMDU, respectively.

When applying APROBA to nasal lesions, the default provisional parameter values in APROBA were used for the 5th percentile (lower confidence limit, LCL) and 95th percentile (upper confidence limit, UCL) of the lognormal distribution for the HD_M^I components (Table 3) other than the POD, based on the analysis inputs listed in Table 2. The confidence limits for the interspecies scaling AF were based on recommendations by IPCS (IOMC ED, 2017) related to inhalation exposure of gases. It is useful to note that the median of this distribution is 1, which is also the DAF for the deterministic IRV. The confidence limits for the interspecies TK/TD AF were based on distributions of ratios of rat and mouse BMDs estimated from the modeling of six endpoints from almost 100 oral NTP studies, totaling almost 1000 datasets (IOMC ED, 2017; Bokkers and Slob, 2007). The confidence limits for the duration extrapolation AF were based on analysis of ratios of subchronic and chronic BMDs for body and liver weight in oral studies on mice and rats (IOMC ED, 2017; Bokkers and Slob, 2005) and were determined to be consistent with the results from multiple analyses of NOAEL ratios in multiple species by both oral and inhalation exposures.

As described in Chiu and Slob (2015) and IOMC ED (2017), the confidence limits for the intraspecies AF were determined by first treating interindividual variability, specifically the interindividual geometric standard deviation, as a random variable, representing the randomness exhibited across chemicals. This variability was separated into toxicokinetic and toxicodynamic components, each demonstrated to be approximately lognormal, and the parameters of each component’s distribution were estimated based on data for approximately 50 chemicals (IOMC ED, 2017; Hattis and Lynch, 2007; Renwick and Lazarus, 1998). The confidence limits for the intraspecies AF were subsequently computed by inverting the distribution of the interindividual geometric standard deviation at the value of incidence I. The resulting intraspecies AF distribution allows extrapolation from the median human (I = 50%) to lower values of I, and thus it differs for different values of I. The limits for nasal lesions were derived using the selected value I of 1%.

Using the parameters described above, APROBA calculated the confidence limits for the $HD_{minimal}^{01}$ distribution for nasal lesions (Table 3). The interval 6.3×10^{-4} mg/m^3 to 8.6×10^{-2} mg/m^3 represents a 90% confidence range for $HD_{minimal}^{01}$. The lower end of that interval, the LCL of 6.3×10^{-4} mg/m^3, can be used as a probabilistic IRV for nasal lesions due to acrolein exposure. This exposure of 6.3×10^{-4} mg/m^3 has an estimated 95% probability of being below the true concentration that causes minimal lesions in the nasal respiratory epithelium in 1% of the general human population. The estimated geometric mean, 7.3×10^{-3} mg/m^3, can be used as a central estimate of the $HD_{minimal}^{01}$ distribution.

3.2.2. Sensitivity analyses—In addition to the primary analysis, a sensitivity analysis was conducted to investigate other options for the distributions of the POD and duration

extrapolation AFs. For the POD AF, dose-response modeling was conducted as an alternative to the NOAEL method. Here, a Bayesian model averaging method was used to account for the minimal-to-maximal dose-response pattern. This method informs uncertainty in estimating the BMD due to this pattern by applying prior distributions to the model parameters (Wheeler et al., 2020). Multiple types of lesions in the nasal epithelium were observed in the Dorman et al. (2008) study, so one of these types needed to be selected for modeling. The lateral wall, especially at level II, was noted as being one of the most sensitive locations for acrolein-induced nasal lesions. Mild respiratory epithelial hyperplasia at this site was first observed after 4 days of exposure to ≥0.6 ppm. The incidence of nasal lesions at this site assessed at exposure day 65 was selected for modeling because it was considered the most sensitive endpoint and was observed after 60 days post exposure. Incidence of level II lateral wall effects used in the dose-response modeling was 0/12 at 0 and 0.2 ppm and 12/12 at 0.6 and 1.8 ppm. The BMDL and BMDU were computed from the dose-response modeling of this effect using the model averaging option in EPA's Benchmark Dose Software (BMDS) version 3.1 (U.S. EPA, 2019), with a 50% extra risk (ER) BMR to correspond to the M used for quantal-deterministic endpoints. After the analysis, doses were adjusted for the dosing regimen of 6 hr/day, 5 days/week, and were subsequently converted from the ppm values reported in Dorman et al. (2008) to mg/m^3, using the conversion factor 1 ppm = 2.3 mg/m^3, to obtain the BMDL and BMDU in mg/m^3.

The confidence ranges from the model averaging analysis were narrower (by about 45%) than for the NOAEL (Table 4), possibly because, given the pronounced minimal-to-maximal response pattern, the priors in the model averaging analysis strongly defined the dose-response curves that were averaged, thus yielding lower uncertainty.

Regarding the duration extrapolation AF, as discussed in Section 3.1 most incidence of nasal lesions in Dorman et al. (2008) occurred at early exposure days, and for some types of lesions incidence decreased at later exposure days. Therefore, it is possible that the nasal lesions resolve at later timepoints for many animals in the population, implying that chronic exposure to acrolein may not result in a substantial increase in the incidence of nasal lesions compared to subchronic exposure. This would indicate that the duration extrapolation AF for nasal lesions may not require as much uncertainty as is represented in the provisional distribution provided in APROBA, which estimates subchronic-to-chronic uncertainty for an arbitrary chemical. However, it is also possible that while the nasal lesions investigated in the Dorman et al. (2008) study may resolve, other respiratory/pulmonary effects could arise with longer exposure durations. Given these considerations, as an alternative, APROBA was also applied using a narrower duration extrapolation AF distribution, one that is geometrically half as wide as the provisional distribution and has LCL equal to 1.0 (Table 4, rows "NOAEL-Narrow" and "BMA-Narrow"). One advantage of using this LCL is that the lower 5% tail of the distribution is bounded above by 1.0; thus, according to this distribution, the probability that a subchronic POD is less than a chronic POD is 5%, which is consistent with the assumption that chronic exposure usually yields a lower POD than subchronic exposure. In addition to the narrower distribution, the data were analyzed using a distribution which assumes no uncertainty (i.e., a "degenerate" distribution, using LCL = UCL = 1.0) for the duration extrapolation AF to correspond to the case where no such AF is applied (Table 4, rows "NOAEL-None" and "BMA-None"). This represents the case of least

uncertainty and results in the least variable HD_M^I among all possible duration extrapolation AF distributions, thus providing a lower limit on the duration extrapolation uncertainty.

The parameters listed in Table 2 and the second and fourth columns of Table 3 were used to derive the confidence limits of the $HD_{minimai}^{01}$ distribution for nasal lesions for the different POD and duration extrapolation AF combinations (Table 4, fourth column). The $HD_{minimal}^{01}$ confidence ranges for the two POD types were similar across the duration extrapolation options, with the model averaging cases having slightly higher confidence limits (by up to 15%) and slightly narrower ranges (by about 10–12%) than their NOAEL counterparts. Comparing the $HD_{minimal}^{01}$ confidence limits across the different duration extrapolation AFs, as expected the ranges become narrower as the duration extrapolation AF distribution becomes narrower, decreasing by almost 60% from the default case to the case with no duration extrapolation AF used. In particular, the LCLs increase as this distribution becomes narrower, indicating that the probabilistic IRV increases as quantitative uncertainty in the duration extrapolation distribution decreases. Taken across all possible alternative analyses of the POD and duration extrapolation AF, the probabilistic IRVs, as represented by the LCLs, ranged from approximately 1.15 to 3.5 times higher than the default probabilistic IRV.

As a means of determining where the greatest uncertainty lies, APROBA calculated the percent of the variance that each AF contributes to the HD_m^i distribution (Table 4, columns 5–8). For the quantal-deterministic case with the NOAEL used as the POD and the APROBA-default distribution used for duration extrapolation (primary analysis), the POD AF contributed the least amount of the variance to the $HD_{minimal}^{01}$ distribution, at 5%, and the remaining variance contributed was distributed approximately evenly across the other three AFs, from 28% (interspecies) to 35% (intraspecies). The POD AF had a lower variance than the other AFs because the minimal-to-maximal dose-response pattern provided strong constraints on the ED_{50}. When the narrow distribution was used for duration extrapolation, its contribution decreased to 10%, and the interspecies and intraspecies contributions increased to compensate. When no duration extrapolation AF distribution was used, its contribution decreased to 0%, and the interspecies and intraspecies contributions increased further, with the latter contributing over 50%. It is important to note that the variance for the intraspecies AF depends on the value of incidence I; its variance decreases as I increases (IOMC ED, 2017). Thus, a higher value of I would yield a lower intraspecies variance and would reduce the contribution of the intraspecies AF to the $HD_{minimal}^{01}$ variance. Conversely, a lower value of I would increase the contribution of the intraspecies AF to the $HD_{minimal}^{01}$ variance. Section 4.2 further discusses the effect of I on the $HD_{minimal}^{01}$ variance. For the case where the BMDL from the model averaging analysis was used as the POD, the POD AF contributed a much lower proportion (1–2%) of the variance as for the NOAEL case, possibly because, as noted above, the priors in the Bayesian model averaging method strongly defined the individual dose-response curves that were averaged, thus yielding low uncertainty in the POD distribution.

In the quantal-deterministic case, a 50% ER BMR was used by default due to the effect being histological lesions of minimal severity. However, often in deterministic risk assessment, a BMR lower than 50% ER is used for histopathological endpoints such as nasal

lesions. To demonstrate the application of the HD_M^I method using a lower BMR, nasal lesions were modeled as a quantal-stochastic endpoint. As discussed in Section 2.2, for quantal-stochastic endpoints the value of M represents the probability that a given individual experiences the adverse effect; it is typically set equal to the BMR from the dose-response modeling when a BMDL is used as the POD. In the case of acrolein-induced nasal lesions, a BMR of 10% ER was used because the respiratory epithelial effects (i.e., hyperplasia) at the LOAEL were graded as minimal to mild and thus considered to be minimally biologically significant. Dose-response modeling (using Bayesian model averaging) was used to calculate the confidence limits for the POD distribution (BMDL and BMDU of 0.046 and 0.128 mg/m^3, respectively). Thus, using 1% for the value of incidence I, APROBA was used to estimate the distribution of HD_{10}^{01}, the concentration at which 1% of a general human population has a 10% probability of experiencing minimal lesions in the nasal respiratory epithelium. The resulting values are a central tendency (geometric mean) of 4.0×10^{-3} mg/mg^3, with a 90% confidence range of (3.4×10^{-4}, 4.6×10^{-2}). These values are about 2-fold lower than the values derived from the quantal-deterministic case (GM of 7.3×10^{-3}, 90% CI of 6.3×10^{-4}, 8.6×10^{-2}). However, it should be noted that the two types of quantal endpoints are not directly comparable (Chiu and Slob (2015)), because the “deterministic” case estimates the dose where the specific severity of “minimal” lesions is experienced by a fraction I of the population, whereas the “stochastic” case estimates the dose where there is a 10% probability of experiencing “minimal” lesions for a fraction I of the population. Moreover, according to IOMC ED (2017), histopathological lesions are most appropriately modeled as “deterministic” due to their being generated from an underlying continuous severity score.

4. Discussion

4.1. Comparison of reference values

The probabilistic IRV of 6.3×10^{-4} mg/m^3 was 23% lower than the deterministic IRV of 8.2×10^{-4} mg/m^3 (Fig. 1). Thus, although the two reference values were comparable in magnitude, the probabilistic IRV was slightly more protective. The probability that $HD_{minima}i^{01}$ is lower than the deterministic IRV is 7.2%; in other words, the deterministic IRV is approximately a 93% lower bound for the $HD_{minimal}^{01}$

The probabilistic and deterministic IRVs can also be compared to inhalation reference values derived by other state and federal agencies (Fig. 2 and Table A1). The chronic reference values derived by OEHHA and TCEQ were 3.5×10^{-4} mg/m^3 and 2.7×10^{-3} mg/m^3, respectively. The probabilistic and deterministic IRVs are reasonably consistent with these values, falling directly between them. EPA/IRIS’s 2003 assessment of acrolein (U.S. EPA, 2003) obtained a chronic inhalation reference value of 2.0×10^{-5} mg/m^3. This value is over 10 times lower than the other chronic reference values, in part because it was based on an older study (Feron et al., 1978) which required the use of an uncertainty factor of 3 to account for use of a LOAEL instead of a NOAEL and a full value of 10 versus 3 for the animal to human UF (UF_A). The current analysis reduced the UF_A because dosimetric modeling in deriving the POD_{HEC} accounted for physiological differences.

A number of reference values were derived by other agencies for shorter exposure durations, ranging from acute to subchronic (Fig. 2 and Table A1). Because they applied to a shorter exposure duration, the majority of these values were above the deterministic and probabilistic IRVs. For example, TCEQ derived a 24-hour reference value of 1.1×10^{-2} mg/m^3, although their reference value was higher in part because it was based on a human study and thus did not require the application of the interspecies UF. However, a minimum risk level derived by ATSDR for exposure from 15 to 365 days was much lower (9.0×10^{-5} mg/m^3) than the deterministic and probabilistic IRVs, partly because it was based on the same study (Feron et al., 1978) as the 2003 IRIS assessment. Also, CalEPA derived an 8-hour reference exposure level (REL) that fell between the probabilistic and deterministic IRVs (7.0×10^{-4} mg/m^3). This REL was based on the (Dorman et al., 2008) study and used the same POD as the IRVs; however, it was derived using a different dose conversion method and an additional toxicokinetic UF. Of note, except for the ATSDR 15–365 day value, all of the shorter duration reference values fall between the $HD_{minimal}^{01}$ LCL and UCL, as demonstrated in Fig. 2, and thus were within the middle 90% confidence range of the $HD_{minimal}^{01}$ distribution. Details on the derivation of these reference values along with the IRVs are provided in Table A1.

4.2. Choice of target human incidence I

The choice of target human incidence I is not fixed and may be varied according to the needs of the risk assessor or risk manager. For example, one can repeat the procedure above for $HD_{minimal}^{50}$, the concentration at which 50% (half) of the population would be expected to develop ("minimal") nasal lesions. This would yield a 90% confidence range from 9.8×10^{-3} mg/m^3 to 0.51 mg/m^3, and the geometric mean, 7.1×10^{-2} mg/m^3, can be used as a central estimate of $HD_{minimal}^{50}$. For illustration, Table 5 lists the median, LCL, UCL, and 90% confidence range (expressed as the ratio UCL/LCL) of the $HD_{minimal}^{I}$ distribution for nasal lesions for the several values of I, and Fig. 3 displays how the $HD_{minimal}^{I}$ range changes with log-dose for different values of I for the median and several coverage values for each I Thus, for example, if a risk assessor is interested in the concentration of acrolein that protects 90% of the human population from experiencing nasal lesions, a line could be traced from the y-axis at I = 10% to the curves to determine the parameters of the distribution of $HD_{minimal}^{10}$. The line would intersect the 5% and 95% coverage curves at 2.4×10^{-3} and 0.172 mg/m^3, respectively, thereby defining a range of 90% coverage of $HD_{minimal}^{10}$, and the line would intersect the 50% coverage curve at 0.020 mg/m^3, which would be the median of the $HD_{minimal}^{10}$ distribution.

Observe from Table 5 that the uncertainty in the $HD_{minimal}^{I}$ distribution increases as I decreases. For example, the 90% confidence range, a measure of uncertainty in $HD_{minimal}^{I}$, increases by a factor of about 2, from 72-fold at I = 10% to 137-fold at I = 1%.

4.3. Strengths and limitations of probabilistic approach

This case example of developing an IRV for acrolein-induced nasal lesions demonstrates several advantages of the probabilistic approach over the deterministic approach. For example, one can quantitatively estimate the risk of an effect at the probabilistic IRV using a central estimate, confidence range, or distribution curve, and the proportion of the

population protected can be incorporated into the estimate. This quantification can also be done for any risk at concentrations above or below the probabilistic IRV. Thus, the method allows greater clarity as to the uncertainties in reference value derivations and provides better information for a greater variety of risk management decisions. For example, the trade-off between identifying a target exposure level that would protect a larger proportion of the population and reducing uncertainty in the target exposure level can be explicitly quantified. In the case of acrolein, estimating $HD_{minimal}^{10}$, the concentration at which 90% of the population is protected against experiencing minimal nasal lesions (incidence I = 10%), would yield a distribution with median 0.020 mg/m^3, an LCL of 2.4×10^{-3} mg/m^3, and a UCL/LCL ratio of 72. However, it may be more desirable to protect a larger percent of the population from nasal lesions. To do this, $HD_{minimal}^{01}$ could be used instead (incidence I = 1%), which would protect 99% of the population against experiencing minimal nasal lesions. However, the median would decrease to 0.007 mg/m^3, the LCL to 0.6×10^{-3}, and the UCL/LCL ratio would increase to 137; thus, the additional desired level of protection involves almost twice as much uncertainty. The results of this quantitative uncertainty analysis can assist a risk manager in effectively reporting and communicating the degree of uncertainty.

The use of APROBA for deriving the probabilistic IRV has some limitations. Because it is designed to be endpoint-specific, APROBA does not incorporate uncertainty related to database deficiencies (analogous to the database UF in the deterministic approach), which would require an approach that considers multiple endpoints and toxicity domains. For acrolein, the database is sufficiently broad, so incorporating this type of uncertainty was not necessary. However, many other chemicals have databases that are too limited to ignore this uncertainty. If a user wants a value that is assumed to be protective of all health endpoints for a chemical with missing information on key endpoints or other deficiencies, applying APROBA to such a chemical would require including an additional AF. If wanting to retain the probabilistic distribution for the end-result, the lognormal parameter values for this AF would have to be determined, which would not be a straightforward exercise in many cases. (At this point, research on database deficiencies is limited; see, for example Blackburn et al. (2015) and Evans and Baird (1998)). Alternatively, APROBA could be utilized to derive a distribution of risk-specific doses for well-studied endpoints and then some other adjustment or additional risk management considerations could be employed to account for the deficiencies in the database.

In the case of nasal lesions for acrolein, it may be useful to further investigate the sensitivity of some of the distributions besides those for the POD and duration extrapolation AF. For example, the confidence limits used for the interspecies scaling AF distribution for inhalation exposure, as recommended by IOMC ED (2017), were based on a general assumption because no formal evaluation of uncertainty was available for this factor. This assumption may be reasonable, but it could be investigated further. Additionally, the distributions for human variation are based on a fairly limited dataset on a limited number of chemicals, many of which are pharmaceuticals. While an updated literature search may be useful to some degree to expand the number of chemicals in the database [e.g., Darney et al. (2020)], recent progress on in silico and in vitro approaches to better estimate toxicokinetic and toxicodynamic human variability also show promise [e.g., Chiu et al. (2017) and Ring et

al. (2017)]. Indeed, by viewing the "default" AF distributions in a Bayesian context as "priors," one could conceive of a fully Bayesian approach in which chemical-specific data are used to "update" the priors to produce an updated estimate of the HD_M^I, consistent with the Bayesian approaches advocated by the NRC (2014) and Simon et al. (2016). The systematic evidence map of (Keshava et al., 2020) identified some human controlled exposure studies, and further refinement of the distributions for human variability may benefit from an analysis of those studies (e.g., using random effects models to separate inter-individual variability from measurement error). However, such an analysis is beyond the scope of the current case study.

Another assumption that was made in both the deterministic and probabilistic derivations is that increasing the exposure duration from 6-h/d to 24-h/d will increase the frequency of the histopathological endpoint. In the Acute Exposure Guideline Level (AEGL) program (NRC, 2001), it was assumed that concentration for a sensory irritant was more of a determinant of effect than the duration of exposure or the resulting C × t product. This may be worthy of further investigation when extrapolating for chronic reference values based on many assumptions that are not well tested; however, based on the information at hand this point cannot be further elucidated, and thus traditional extrapolations were applied.

Another issue that may need further development is the decision of which approach to use when applying APROBA to dichotomous endpoints, the quantal-stochastic or quantal-deterministic approach. For acrolein, a well-defined histopathological endpoint (minimally adverse nasal lesions) was used as the critical effect, so it was clear that the quantal-deterministic approach was the more appropriate one to apply. In addition, the minimal-to-maximal response in the nasal lesions data provided strong bounds on the ED_{50}, so there was reasonable confidence that using the NOAEL as the POD provided an adequate estimate of the HD_{miimal}^{01} distribution. However, in other cases it will not be as straightforward to determine which approach to use. Not all dichotomous endpoints fall clearly under either approach. For example, for some developmental endpoints (e.g., some malformations), it could be debated whether the incidence is the result of a "continuum" of variation to which a threshold is applied (quantal-deterministic) or a random process more akin to mutations (quantal-stochastic). Furthermore, it would have to be determined how to communicate and compare the risk-specific doses derived using the two approaches, given that a 1% incidence of a minimally adverse nasal lesion is not directly comparable to a 1% incidence of a 10% risk of developing a nasal lesion.

Also, it should be noted that while the APROBA Excel spreadsheet requires that the HD_M^I components be lognormally distributed, the unified probabilistic framework (IOMC ED, 2017) that it applies does not require this assumption. For acrolein, there does not exist any information indicating departures from lognormality in the AFs, so assuming lognormality was deemed reasonable. Other distributions can be used for any of the components but would require different software. In most cases Monte Carlo resampling approaches would be needed. Furthermore, while the assumption of independence is not necessary, dropping this assumption would require incorporating a proper dependence structure. More research is needed to investigate the possible dependence among the HD_M^I components.

Finally, it should be noted that an HD_M^I can be calculated for any endpoint of concern, not just a single "critical" endpoint. An HD_M^I for other effects could be useful to provide information for evaluating mixtures, where the common effect might not always be the "critical effect" of each chemical individually, or for use in a benefit-cost analysis, where a valuation is easier or greater for an effect other than the "critical effect". This is consistent with advice from the National Academy of Sciences to move towards development of "risk-specific doses" (NRC, 2009). In the case of acrolein, a separate systematic evidence map was performed to identify the most appropriate endpoint to model (Keshava et al., 2020).

5. Conclusions

Overall, this case study demonstrates the application of a probabilistic approach for deriving an IRV, thereby generating a quantitative estimate of the severity, incidence, and uncertainty of effects at a given dose. This work complements the previous work by Chiu et al. (2018), which broadly applied the probabilistic approach to oral reference values, and in addition conducts a number of sensitivity analyses to examine the robustness of the results. As additional case studies are conducted, it is anticipated that derivation of probabilistic reference values will become more routine, thereby providing a richer quantitative characterization of dose-response for use in risk assessment and risk management decision-making.

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Appendix A.: Acrolein Inhalation Reference Values for Exposures to the General Public

See Table A1.

Table A1

Derivation details on acrolein inhalation reference values for exposures to the general public.

Reference Value Type/ Name	Duration	Reference Value		Health Effects	Point of Departure[1]		Uncertainty Factors[2]	Review Status
		mg/ m^3	ppm					
CA-REL (Acute)	1 hr	2.5 × 10^{-3}	1.1 × 10–3	Subjective ocular irritation in humans (Weber-Tschopp et al., 1977; Darley et al., 1960)	0.06 ppm 0.07 ppm	LOAEL LOAEL	Total UF = 60 UF_L = 6 UF_H = 10	Final (OEHHA, 2008)

Reference Value Type/ Name	Duration	Reference Value		Health Effects	Point of Departure[1]		Uncertainty Factors[2]	Review Status
		mg/m^3	ppm					
CA-REL (8-hr)	8 hr	7×10^{-3}	3×10^{-4}	Lesions in the respiratory epithelium in rats (Dorman et al., 2008)	0.2 ppm 0.06 ppm	NOAEL $NOAEL_{HEC}$	Total UF = 200 UFs = $10^{1/2}$ UF_A: 2 (TK), $10^{1/2}$ (TD) UF_H = 10	
TCEQ ReV (Acute)	1 hr	1.1×10^{-3}	4.8×10^{-4}	Eye, nose and throat irritation and decreased respiratory rate in humans (Weber-Tschopp et al., 1977)	0.3 ppm	LOAEL	Total UF = 63[3] UF_L = 6.3 UF_H = 10	Final (TCEQ, 2016)
TCEQ ReV (24-hr)	24-hr	1.1×10^{-3}	4.8×10^{-4}					
ATSDR-MRL (1–14 d)	1–14 d	7×10^{-3}	3×10^{-4}	Decrease in respiratory rate, nose and throat irritation (Weber-Tschopp et al., 1977)	0.3 ppm	LOAEL	Total UF = 100 UF_L = 10 UF_H = 10	Final (Agency for Toxic Substances and Disease
ATSDR-MRL (15–365 d)	15 d – 1 yr	9×10^{-5}	4×10^{-5}	Nasal epithelial metaplasia in rats (Feron et al., 1978)	0.012 ppm	$LOAEL_{HEC}$	Total UF = 300 UF_L = 10 UF_A = 3 UF_H = 10	Registry (ATSDR), 2007)
TCEQ ReV (Chronic)	Chronic	2.7×10^{-3}	1.2×10^{-3}	Mild hyperplasia and lack of recovery of the respiratory epithelium (Dorman et al., 2008)	0.2 ppm 0.036 ppm 0.036 ppm	NOAEL $NOAEL_{ADJ}$ $NOAEL_{HEC}$	Total UF = 30 UF_A = 3 UF_H = 10	Final (TCEQ, 2016)
CA-REL (Chronic)	Chronic	3.5×10^{-4}	1.5×10^{-5}	Lesions in respiratory epithelium (Dorman et al., 2008)	0.2 ppm 0.036 ppm 0.03 ppm	NOAEL $NOAEL_{ADJ}$ $NOAEL_{HEC}$	Total UF = 200 UF_A: 2 (TK), $10^{1/2}$ (TD) UF_H = 10 UFs = $10^{1/2}$	Final (OEHHA, 2008)
RfC (IRIS)	Chronic	2×10^{-5}	8.7×10^{-6}	Slight nasal effects (Feron et al., 1978)	0.9 mg/m^3 0.16 mg/m^3 0.02 mg/m^3	LOAEL $LOAEL_{ADJ}$ $LOAEL_{HEC}$	Total UF = 1000 UF_A = 3 UF_H = 10 UF_S = 10 UF_L = 3	Final (U.S. EPA, 2003)
Deterministic IRV	Chronic	8.2×10^{-4}	3.6×10^{-4}	Lesions in respiratory epithelium (Dorman et al., 2008)	0.46 mg/m^3 0.082 mg/m^3 0.082 mg/m^3	NOAEL $NOAEL_{ADJ}$ $NOAEL_{HEC}$	Total UF = 100 UF_A = 3 UF_H = 10 UF_S = 3	

Reference Value Type/ Name	Duration	Reference Value		Health Effects	Point of Departure[1]	Uncertainty Factors[2]	Review Status
		mg/m^3	ppm				
Probabilistic IRV	Chronic	6.3×10^{-4}	2.7×10^{-4}		See Table 2	$UF_S = 3$ See Table 3	

[1] $LOAEL_{adj}$ – duration-adjusted LOAEL; $NOAEL_{adj}$ – duration-adjusted NOAEL.

[2] UF_A – Animal to Human Factor; UF_H – Inter-individual Human Variability Factor; UF_S – Subchronic to Chronic Factor; UF_L – LOAEL to NOAEL Factor.

[3] UF_L = 6.3 based on (Alexeeff et al., 2002).

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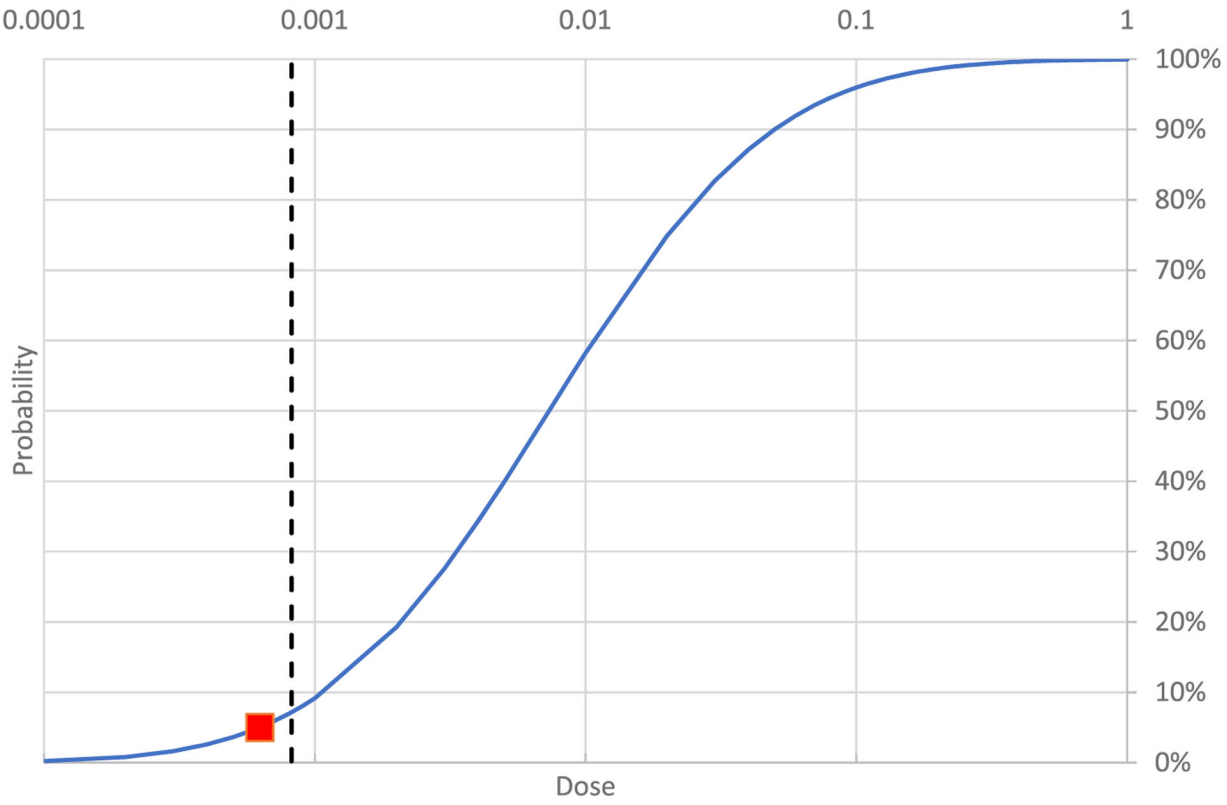

Fig. 1.

Graph of cumulative distribution function of the calculated uncertainty in the $HD_{minimal}^{01}$ for nasal lesions. The red square on the curve represents the probabilistic IRV, defined as the lower 5% confidence bound, and the dotted black line represents the dose value equal to the deterministic IRV, which intersects at approximately the 7% lower confidence level.

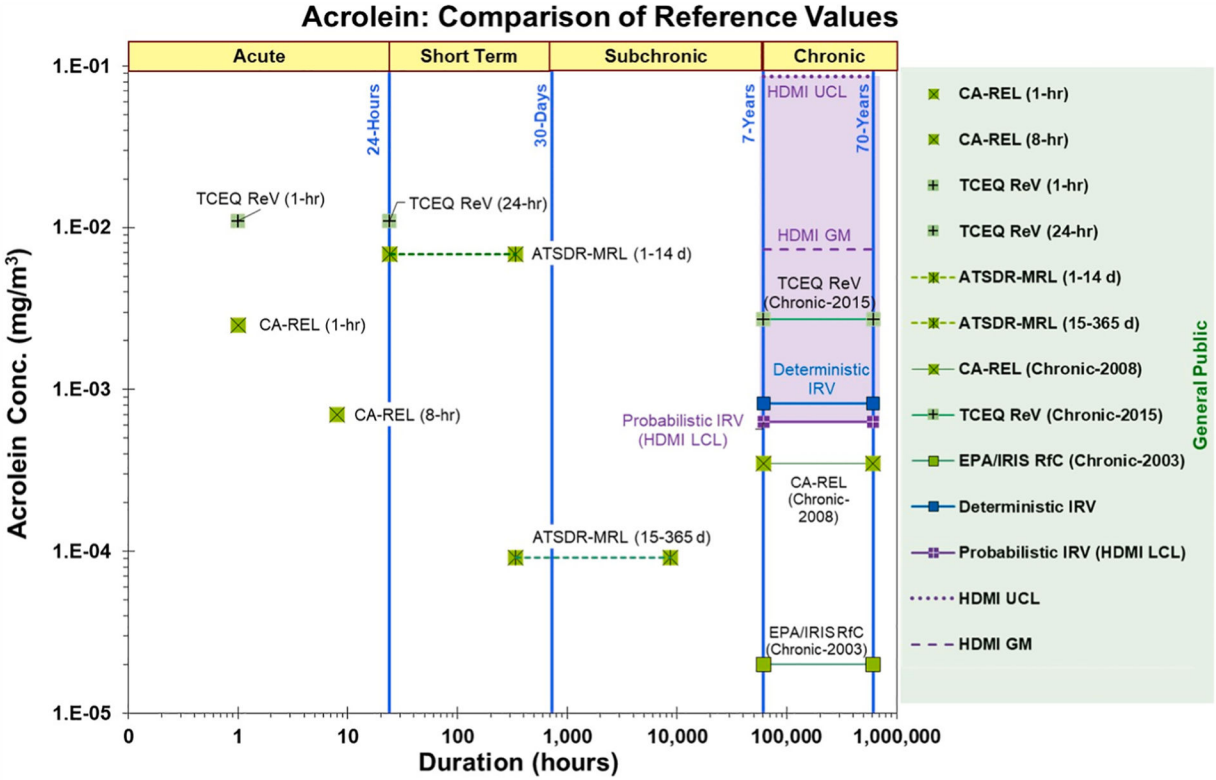

Fig. 2.

Comparison of acrolein general public health reference values to both the deterministic and probabilistic IRVs. The probabilistic IRV is equal to the lower confidence limit (LCL) of the human dose of minimal incidence ($HD_{minimal}^{01}$, denoted “HDMI” in figure) in 1% of the population, with $HD_{minimal}^{01}$ upper confidence limit (UCL) and geometric mean (GM) also indicated in the figure; the shaded band from the LCL to the UCL represents the 90% confidence range of the $HD_{minimal}^{01}$ distribution. Line segments signify the duration of individual reference values.

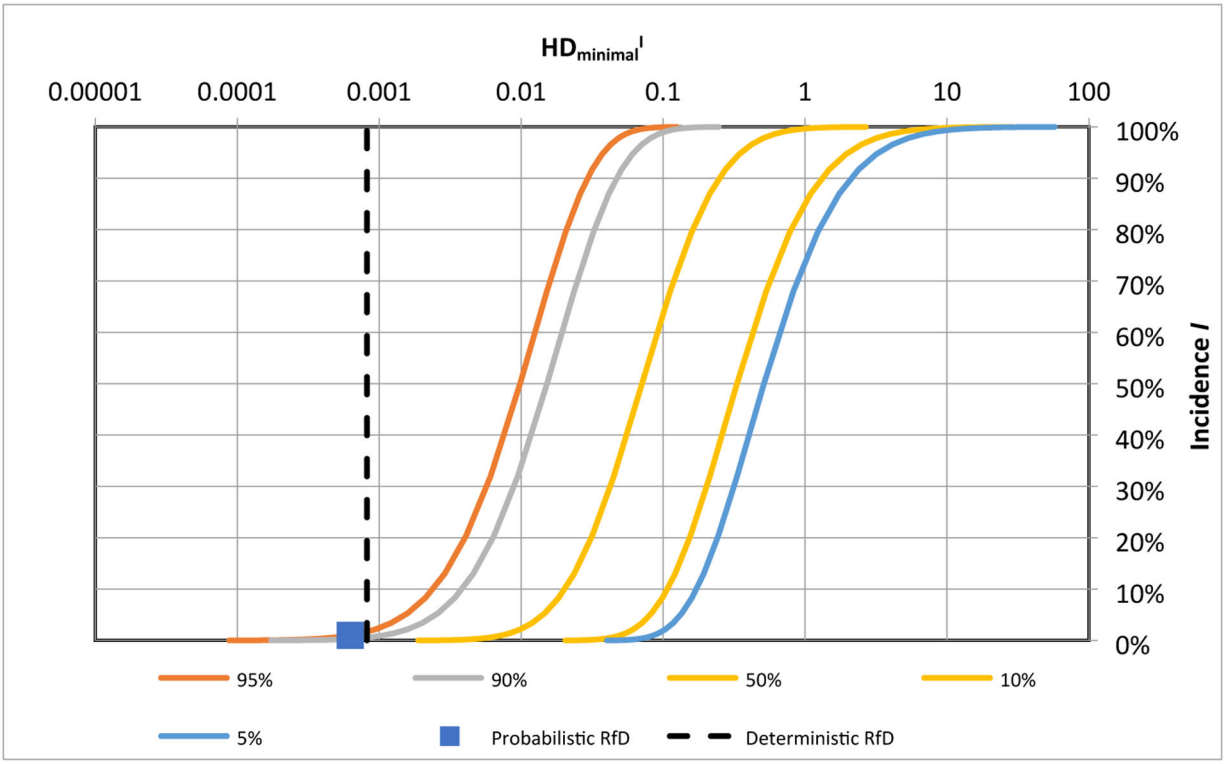

Fig. 3.

$HD_{minimal}{}^{I}$ distribution for the median and several coverage values for nasal lesion incidence in male rats.

Table 1

Components of deterministic inhalation reference value.

Description	Value	Comments
POD_{HEC} (mg/m^3)	0.082	DAF = 1; see Keshava et al. (2020)
Interspecies (UF_A)	3 ($10^{1/2}$)	Applies to uncertainty in interspecies toxicodynamics (see text)
Intraspecies (UF_H)	10	Accounts for human variability in the severity or range of response from any given acrolein exposure amongst different individuals
Duration extrapolation (UF_S)	3 ($10^{1/2}$)	Adjusts for subchronic-to-chronic duration (see text)
LOAEL-to-NOAEL (UF_L)	1	NOAEL was used as POD
Database (UF_D)	1	Database for acrolein was considered complete (see text)
Deterministic IRV (mg/m^3)	8.2×10^{-4}	POD/Composite UF

Table 2

Inputs related to study type, endpoint, and protection goals entered in APROBA for calculating the probabilistic IRV.

Description	Input	Comments
Type of endpoint	Quantal-deterministic	Histopathological endpoint (see text)
Type of POD	BMDL	NOAEL is treated as a lower confidence bound on the ED_{50} (see text)
Route of exposure	Inhalation	Dorman et al. (2008) was an inhalation study
Exposure duration	Subchronic	Dorman et al. (2008) was a 13-week study
Test species	Rat	Dorman et al. (2008) was in rats
Target BMR	50% extra risk	Default for quantal-deterministic endpoint (see Section 2.2; corresponds to M = “minimal severity”)
POD	0.082 mg/m^3	Value of NOAEL, adjusted to continuous exposure from the dosing regimen of 0.46 mg/m^3 for 6 hr/day, 5 days/week.
BMDU	0.246 mg/m^3	Value of LOAEL, adjusted to continuous exposure from the dosing regimen of 1.38 mg/m^3 for 6 hr/day, 5 days/week.
Incidence I	1%	Protection of large fraction (99%) of the population.

Table 3

Input distributions and risk-specific dose output for acrolein-induced nasal lesions.

Component[1]	LCL	GM	UCL
POD[2] (mg/m^3)	0.082	0.142	0.246
AF for Interspecies scaling	0.5	1.0	2.0
AF for Interspecies TK/TD	0.33	1.0	3.0
AF for Duration Extrapolation	0.5	2.0	8.0
AF for Intraspecies at 1% incidence	2.24	9.69	41.88
$HD_{minimal}^{01}$ (mg/m^3)	6.3×10^{-4}	7.3×10^{-3}	8.6×10^{-2}

[1] LCL: Lower 5% confidence limit; GM: Geometric mean = median under lognormal approximation; UCL: Upper 95% confidence limit; POD: point of departure; AF: adjustment factor; TK/TD: toxicokinetic/toxicodynamic; $HD_{minimal}^{01}$: Human dose that causes at least "minimal" nasal lesions in the 1% most sensitive part of the human population distribution. Sources: See text for POD. Other factors from IOMC ED (2017).

[2] The POD distribution is estimated for the POD_{HEC}.

Table 4

Sensitivity analyses results in comparison to primary analysis.

APROBA Analyses[a]	POD distribution[b]	Duration AF distribution[b]	$HD_{minimal}{}^{01}$[c]	Adjustment Factor % contribution to uncertainty[d]			
				POD	Interspecies[e]	Duration	Intraspecies
NOAEL[f] - APROBA default (primary analysis)	0.082–0.246	0.5–8.0	6.3×10^{-4}–8.6×10^{-2} (137)	5%	28%	32%	35%
NOAEL - Narrow		1.0–4.0	8.6×10^{-4}–6.3×10^{-2} (73)	7%	36%	10%	46%
NOAEL - None		1.0–1.0	19.2×10^{-4}–11.2×10^{-2} (58)	7%	41%	0%	52%
BMA[fg] - APROBA default	0.122–0.199	0.5–8.0	7.2×10^{-4}–9.0×10^{-2} (124)	1%	29%	33%	37%
BMA–Narrow		1.0–4.0	9.9×10^{-4}–6.5×10^{-2} (65	1%	39%	11%	49%
BMA - None		1.0–1.0	22.4×10^{-4}–11.6×10^{-2} (52)	2%	43%	0%	55%

[a] POD - Duration adjustment combination.

[b] Lower confidence limit (LCL) - upper confidence limit (UCL), in mg/m^3.

[c] Confidence intervals: LCL-UCL; value in parentheses is confidence interval width expressed by the ratio of UCL to the LCL. For all cases, the LCL and UCL are presented as multiples of 10^{-4} and 10^{-2}, respectively, for ease of comparison.

[d] The percent uncertainty (variance) contributed by every component to the $HD_{minimal}{}^{01}$ distribution.

[e] The percent contribution presented for the interspecies AF was summed across the interspecies scaling and TK/TD AFs.

[f] M = 50% extra risk. After the analysis, doses were adjusted for the dosing regimen of 6 hr/day, 5 days/week, and were subsequently converted from the ppm values reported in Dorman et al. (2008) to mg/m^3, using the conversion factor 1 ppm = 2.3 mg/m^3, to obtain the BMDL and BMDU in mg/m^3.

[g] "BMA": Bayesian model averaging, for dichotomous data. Incidence of level II lateral wall effects used in this analysis was 0/12 at 0 and 0.2 ppm and 12/12 at 0.6 and 1.8 ppm.

Table 5

The median, LCL, UCL, and 90% confidence range (expressed as UCL/LCL) of the $HD_{minimal}^{I}$ distribution for nasal lesions for the several values of I (where I is the percentage of the population that develops nasal lesions).

I	LCL (mg/m^3)	Median (mg/m^3)	UCL (mg/m^3)	UCL/LCL
1%	0.6×10^{-3}	0.007	0.086	137
5%	1.5×10^{-3}	0.014	0.133	86.9
10%	2.4×10^{-3}	0.020	0.172	71.6
50%	9.8×10^{-3}	0.071	0.513	52.2