



Case Study: Application of ARPOBA to Acrolein and Chloroform

By Todd Blessinger

**Workshop: Advancing Quantitative Analysis in Human Health
Assessments through Probabilistic Methods**

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- **Summarize unified probabilistic framework and Approximate Probability Analysis (APROBA)**
- **Acrolein case study (Blessinger et al., 2020)**
 - Endpoint: nasal lesions from Dorman et al. (2008)
 - Deterministic inhalation reference value (IRV)
 - Application of APROBA and probabilistic IRV
 - Sensitivity analysis
 - Risk-specific dose
- **Chloroform case study**
 - Summary of APROBA application
 - Comparison of probabilistic and deterministic reference concentrations (IRVs)



Probabilistic Uncertainty Analysis

- **WHO/IPCS has released guidance on the application of probabilistic approach to uncertainty when deriving reference values through the unified probabilistic framework.**
 - Focuses on quantitative evaluation of uncertainties, particularly probabilistic reference values.
 - Recommended by NRC (1994, 2009, 2014).

- **Limitations of current *deterministic* method for applying uncertainty factors**
 - Cannot quantitatively calculate risk at the reference value.
 - Not possible to estimate the probability of an adverse effect occurring at doses/concentrations above the reference value.
 - Lack of flexibility: the dose yielding a pre-specified risk cannot be readily assessed.



Unified Probabilistic Framework

- **Unified probabilistic framework focuses on deriving HD_M^I , the human dose (HD) associated with an effect of some magnitude (M) and population incidence (I)**
- **Example:**

The oral reference dose (RfD) is the human dose at which 1% of the population experiences a decrease in liver weight of 5% or greater.

Incidence, I

Magnitude, M

Human
Dose, HD



Unified Probabilistic Framework and APROBA

- $HD_M^I = \frac{POD}{AF_1 \times \dots \times AF_k}$
- **POD is a BMDL or NOAEL**
- **AF_i 's are “assessment factors”**
- **Under probabilistic framework, each AF (and POD) is treated as a random variable with a probability distribution.**
- **HD_M^I is thus also a random variable whose distribution depends on the values of M and I**
- **In Approximate Probabilistic Analysis (APROBA) tool, all components are assumed to be log-normally distributed and independent.**
- **Endpoint-specific: does not take database deficiencies into account**



Acrolein

- **Acrolein assessed by multiple entities, such as IRIS (2003) and ATSDR (2024 draft).**
- **Recent assessments (TCEQ, OEHHA, ATSDR) used lesions in the nasal epithelium (i.e., nasal lesions) in a 13-week rat inhalation study by Dorman et al. (2008) to derive a chronic inhalation toxicity value.**
- **Lesions observed in multiple locations in the nasal epithelium, most of which exhibited near-minimal-to-near-maximal dose response patterns.**
- **The lateral wall at level II was one of the most sensitive locations for acrolein-induced nasal lesions.**
 - Incidence of at least minimal severity:

Dose (mg/m ³)	0	0.082	0.246	0.738
Incidence	0 / 12	0 / 12	12 / 12	12 / 12



Acrolein: Deterministic IRV

- **NOAEL = 0.082 mg/m³ & LOAEL = 0.246 mg/m³**
- **Deterministic inhalation reference value (IRV):**

Component	Value
POD (mg/m ³)	0.082
Interspecies (UF _A)	3
Intraspecies (UF _H)	10
Duration extrapolation (UF _S)	3
LOAEL-to-NOAEL (UF _L)	1
Database (UF _D)	1

- **Deterministic IRV = $\frac{0.082}{100} = 8.2 \times 10^{-4}$ mg/m³**



Acrolein: APROBA Application

- **Human incidence I = 1% used.**
- **Nasal lesions treated as quantal-deterministic (measured on graded severity scale).**
 - POD = ED50, so M = “minimal severity”
- **NOAEL and LOAEL provide strong constraints on ED50.**
 - Use BMDL as POD, with BMDL = NOAEL & BMDU = LOAEL.
- **Provisional parameter values used for other AFs, based on historical data.**



Acrolein: APROBA Application

- **APROBA inputs**

Description	Input
Type of endpoint	Quantal-deterministic
Type of POD	BMDL
Route of exposure	Inhalation
Exposure duration	Subchronic
Test species	Rat
Target BMR	50% ER
POD	0.082 mg/m ³
BMDU	0.246 mg/m ³
Incidence I	1%



Acrolein: APROBA Application

➤ HD_{minimal}^{01} component distributions and risk-specific dose output

Component	LCL ^a	Median ^a	UCL ^a
POD (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 (1% incidence)	2.24	9.69	41.88
$HDMI_{\text{minimal}}^{01}$ (mg/m ³)	6.3×10^{-4}	7.3×10^{-3}	8.6×10^{-2}

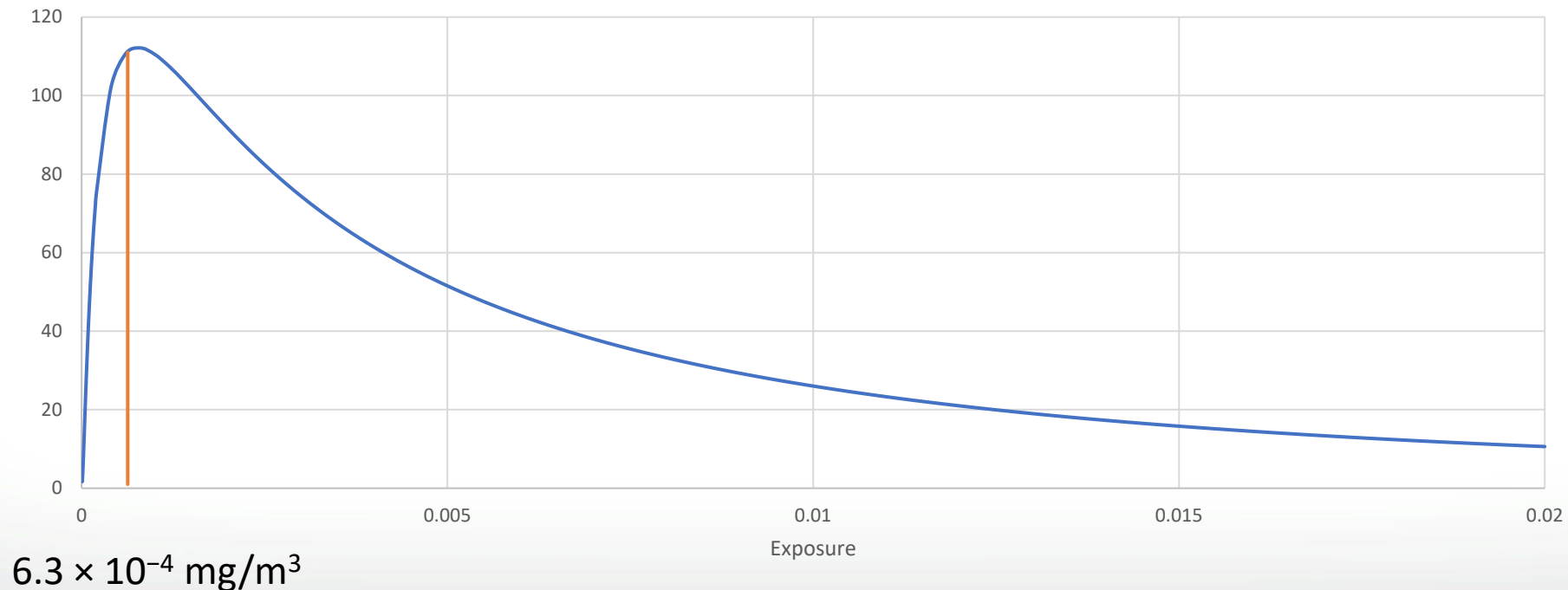
^aLCL = lower 5% confidence limit; median = 50th percentile; UCL = upper 95% confidence limit

➤ HD_{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



Acrolein: Probabilistic IRV

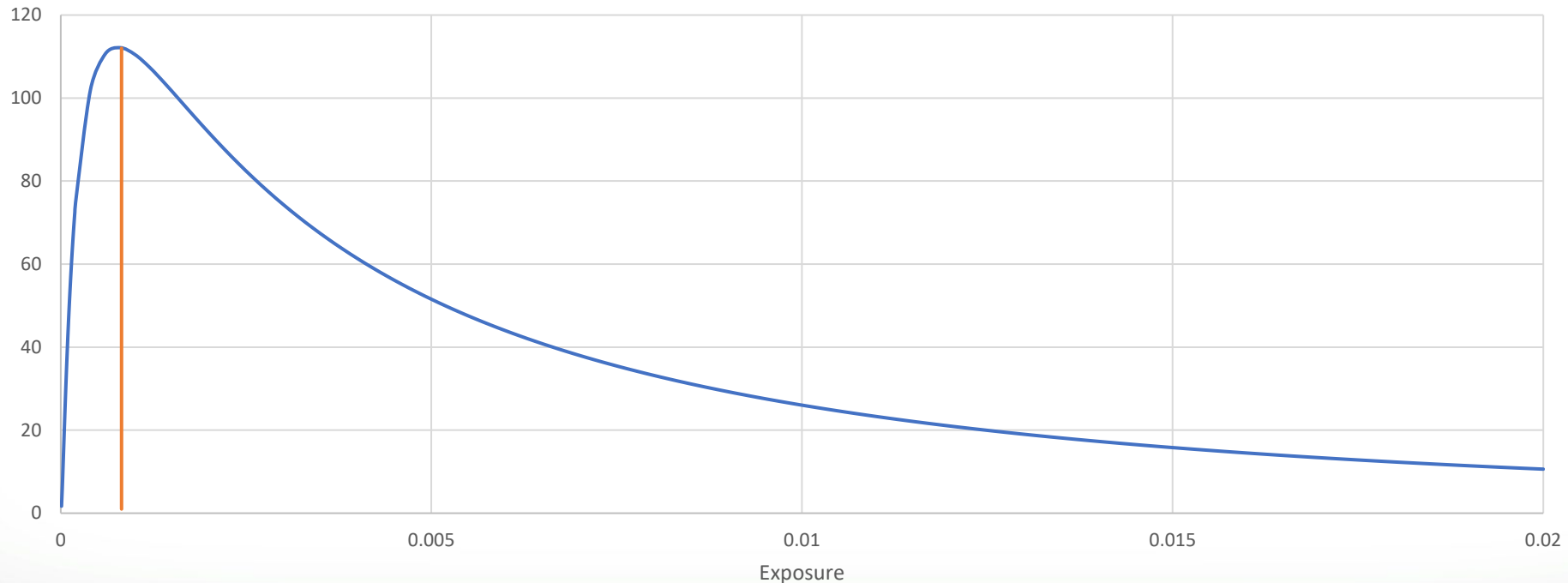
- **LCL (5th percentile) of HD_{minimal}^{01} distribution, $6.3 \times 10^{-4} \text{ mg/m}^3$, can be used as the probabilistic IRV for nasal lesions.**
 - This exposure of $6.3 \times 10^{-4} \text{ mg/m}^3$ has an estimated 95% probability of being below the true concentration that causes minimal lesions in the nasal respiratory epithelium in 1% of the general human population.





Acrolein: Deterministic IRV

- **Deterministic IRV, $8.2 \times 10^{-4} \text{ mg/m}^3$, is 30% higher than the probabilistic IRV.**
 - Represents the 7th percentile of the $\text{HD}_{\text{minimal}}^{01}$ distribution and thus provides 93% coverage.



$8.2 \times 10^{-4} \text{ mg/m}^3$



Acrolein: Sensitivity Analysis

➤ **Duration AF:**

- Chronic exposure to acrolein may not result in a substantial increase in the incidence of nasal lesions compared to subchronic exposure.
- Duration extrapolation AF for nasal lesions may not require as much uncertainty as is represented in the provisional distribution provided in APROBA.

➤ **POD AF:**

- Dose-response modeling conducted as an alternative to NOAEL method.
- Bayesian model averaging in BMDS used to account for minimal-to-maximal pattern.



Acrolein: Sensitivity Analysis

➤ **Confidence limits of input and HD_{minimal}^{01} distributions for sensitivity analysis**

APROBA Analysis	POD Distribution	Duration AF Distribution	HD_{minimal}^{01}	Confidence Range (UCL/LCL)
NOAEL - APROBA default	0.082 - 0.246	0.5 - 8.0	$6.3 \times 10^{-4} - 8.6 \times 10^{-2}$	137
NOAEL - Narrow	0.082 - 0.246	1.0 - 4.0	$8.3 \times 10^{-4} - 6.3 \times 10^{-2}$	73
NOAEL - None	0.082 - 0.246	1.0 - 1.0	$19.2 \times 10^{-4} - 11.2 \times 10^{-2}$	58
BMA ^a - APROBA default	0.122 - 0.199	0.5 - 8.0	$7.2 \times 10^{-4} - 9.0 \times 10^{-2}$	124
BMA - Narrow	0.122 - 0.199	1.0 - 4.0	$9.9 \times 10^{-4} - 6.5 \times 10^{-2}$	65
BMA - None	0.122 - 0.199	1.0 - 1.0	$22.4 \times 10^{-4} - 11.6 \times 10^{-2}$	52

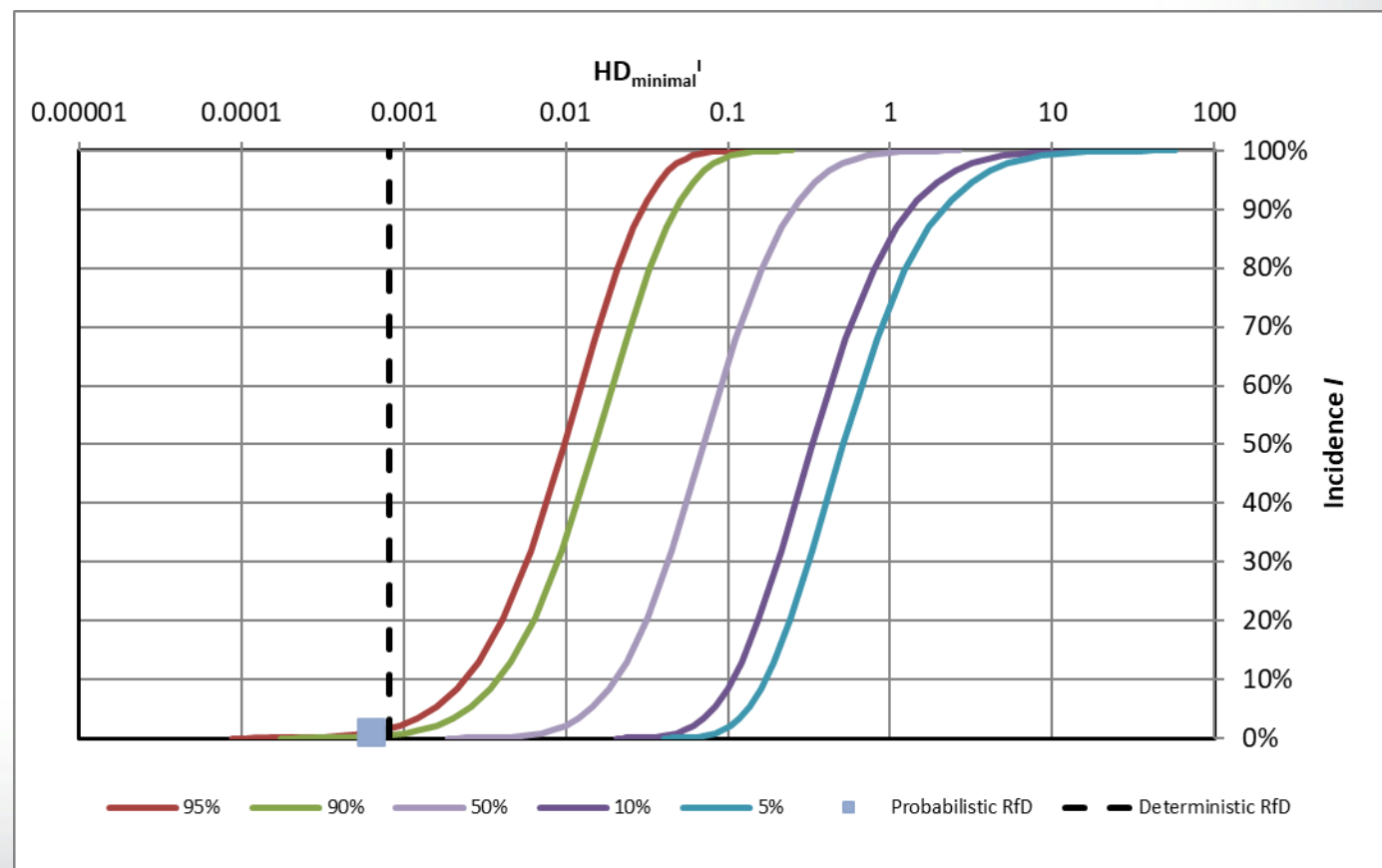
^aBMA = Bayesian model averaging



Acrolein: Risk-Specific Dose

- Target human incidence I can be varied according to the needs of the risk assessor.

I	LCL	Median	UCL	UCL/LCL
0.5%	0.4×10^{-3}	0.006	0.074	166
1%	0.6×10^{-3}	0.007	0.086	137
5%	1.5×10^{-3}	0.014	0.133	87
10%	2.4×10^{-3}	0.020	0.172	72





Chloroform: APROBA Application

- To ground the evaluation of probabilistic reference values in current efforts, this case study uses datasets being considered in an in-development draft IRIS toxicological review of chloroform by inhalation.
- **Animal studies reported developmental, liver, and kidney effects from exposure to chloroform by inhalation.**
 - Histopathological endpoints (liver, kidney), liver weight (continuous), and developmental endpoints.
- **APROBA was applied to the endpoints from these studies that could be used to derive a BMDL or NOAEL as the POD (i.e., 21 datasets, using administered exposure).**
 - Human incidence $I = 1\%$ was used in primary analysis.
- **Primary analysis for dichotomous endpoints:**
 - Quantal-deterministic for histopathological endpoints
 - Quantal-stochastic for developmental endpoints. $M = \text{BMR of } 5\% \text{ ER.}$
- **Quantal-stochastic also applied to histopathological endpoints for comparison to deterministic IRVs.**
- **Sensitivity analysis conducted by adjusting remaining TK/TD uncertainty and POD uncertainty.**



Chloroform: APROBA Application

➤ **Principal effects on variability:**

- POD type: In most cases, a NOAEL yielded more HD_M^I uncertainty than a BMDL because its AF distribution had higher variability.
- Duration type: Subchronic studies yielded more HD_M^I uncertainty than chronic studies because only the former required additional uncertainty from study duration.

➤ **For comparison to probabilistic IRVs, deterministic IRVs were calculated excluding database uncertainty.**

➤ **Probabilistic IRVs were lower than their deterministic counterparts for non-subchronic endpoints and higher for subchronic endpoints.**

- Three subchronic endpoints had probabilistic IRVs that were 3-4 times higher than their deterministic counterparts.
- The probabilistic and deterministic IRVs differed by less than threefold for all the other endpoints, both subchronic and chronic.



Chloroform: APROBA Application

- **Ranges of probabilistic IRVs and deterministic IRVs for endpoints within each toxicity**

Toxicity	Probabilistic IRV range	Endpoint with lowest probabilistic IRV	Deterministic IRV range	Endpoint with lowest deterministic IRV
Developmental	0.634-4.32	Post-implantation loss in rats	1.65-5.07	Post-implantation loss in rats
Liver	0.0157-0.380	Hepatic lesions in female mice	0.00743-0.610	Hepatic lesions in female mice
Kidney	0.0553-0.611	Kidney lesions in male mice	0.0170-1.20	Kidney lesions in male rats



Conclusions

- **Case studies demonstrate greater flexibility using the probabilistic approach to deriving reference values.**
 - Probabilistic approach allows estimate of risk at reference value and derivation of risk-specific dose.
- **Probabilistic reference values were not very different from the deterministic reference values in these case studies.**
- **Determination of human incidence I requires input from the risk assessor and/or risk manager.**
 - Balance between level of protection and magnitude of uncertainty.
- **Considerations for more regular application:**
 - Development of standard practices.
 - Determination of magnitude M , incidence I , and confidence level
 - Level of effort and resourcing (at least in near term)



Acknowledgements & References

- **Acrolein co-authors: Allen Davis, Weihsueh Chui, John Stanek, George Woodall, Jeff Gift, Kris Thayer, David Bussard**
- **Chloroform team: Margaret Pratt, Andre Weaver (co-managers), Christine Cai**
- **WHO/IPCS, 2017. Guidance document on evaluating and expressing uncertainty in hazard characterization.**
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