Case Study: Application of ARPOBA to Acrolein and Chloroform

By Todd Blessinger

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

10/07/24

Office of Research and Development
Center for Public Health and Environmental Assessment

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Outline

- **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)

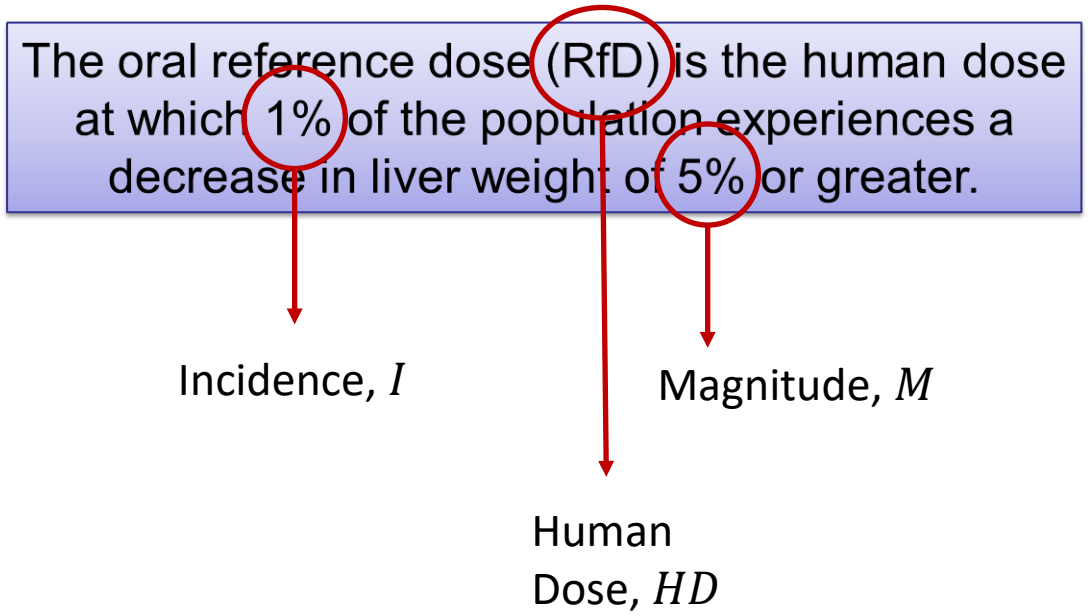
Probabilistic Uncertainty Analysis

- **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 $\mathrm{HD}_M{}^I$, the human dose (HD) associated with an effect of some magnitude (M) and population incidence (I)**
- **Example:**



Unified Probabilistic Framework and APROBA

- $\mathrm{HD}_M{}^I = \frac{\mathrm{POD}}{\mathrm{AF}_1 \times \ldots \times \mathrm{AF}_k}$
- **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.**
- **$\mathrm{HD}_M{}^I$ 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/m^3 & LOAEL = 0.246 mg/m^3**
- **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/m^3

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**

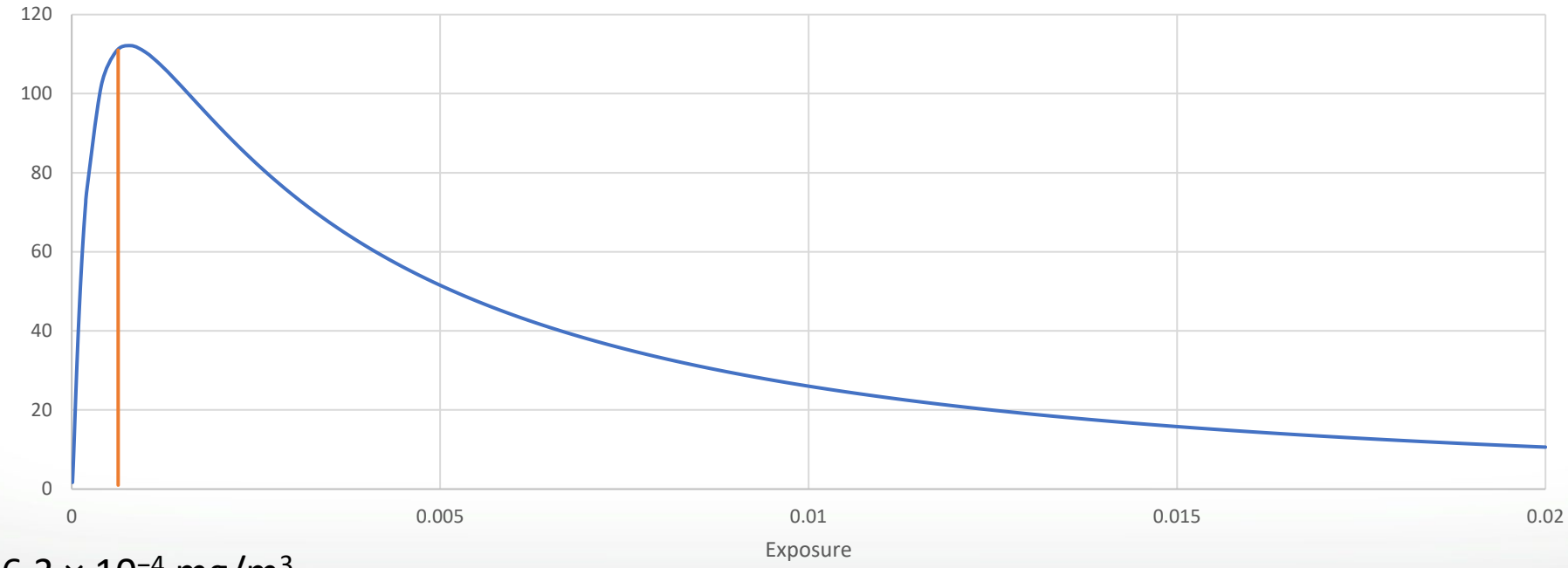
Component	LCL[a]	Median[a]	UCL[a]
POD (mg/m^3)	0.082	0.142	0.246
AF for interspecies scaling	0.5	1.0	2.0
AF for interspecies TK/TD	0.33	1.0	3.0
AF for duration extrapolation	0.5	2.0	8.0
AF for intraspecies (1% incidence)	2.24	9.69	41.88
$HDMI_{minimal}^{01}$ (mg/m^3)	6.3×10^{-4}	7.3×10^{-3}	8.6×10^{-2}

[a]LCL = 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

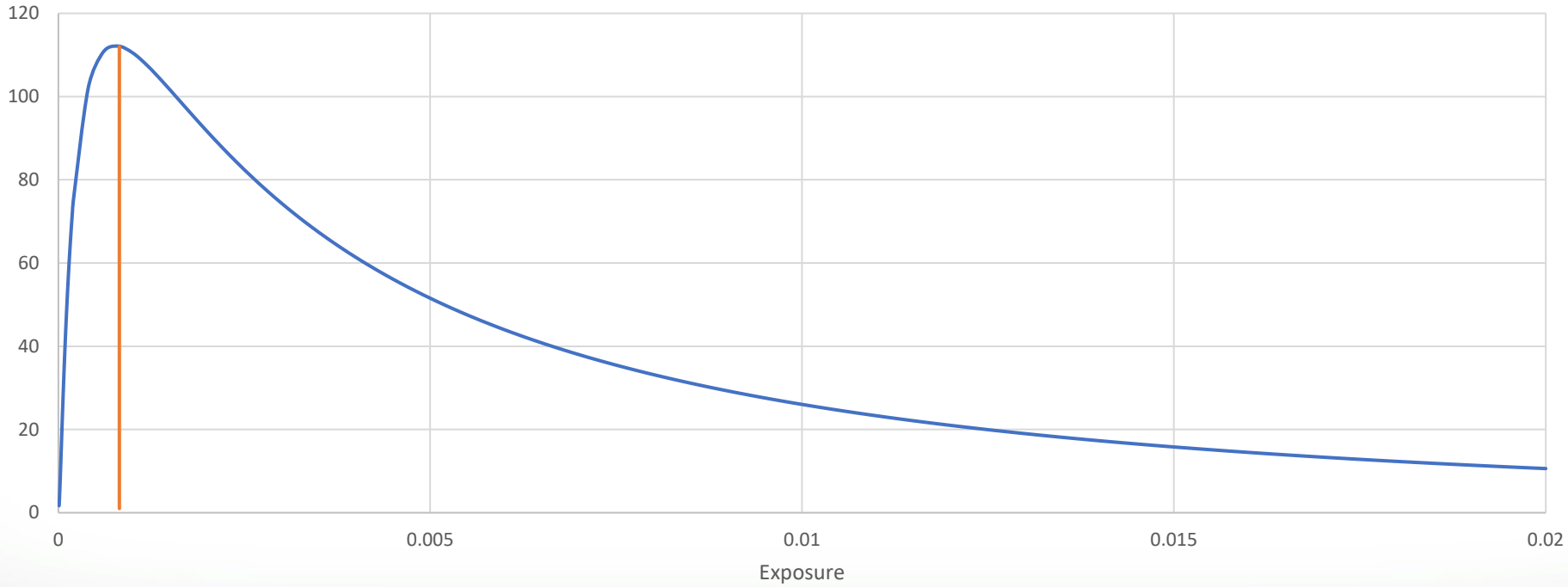
- **LCL (5th percentile) of $HD_{minimal}^{01}$ distribution, 6.3×10^{-4} mg/m^3, can be used as the probabilistic IRV for nasal lesions.**
  - This exposure of 6.3×10^{-4} mg/m^3 has an estimated 95% probability of being below the true concentration that causes minimal lesions in the nasal respiratory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



6.3×10^{-4} mg/m^3

Acrolein: Deterministic IRV

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



8.2×10^{-4} 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**

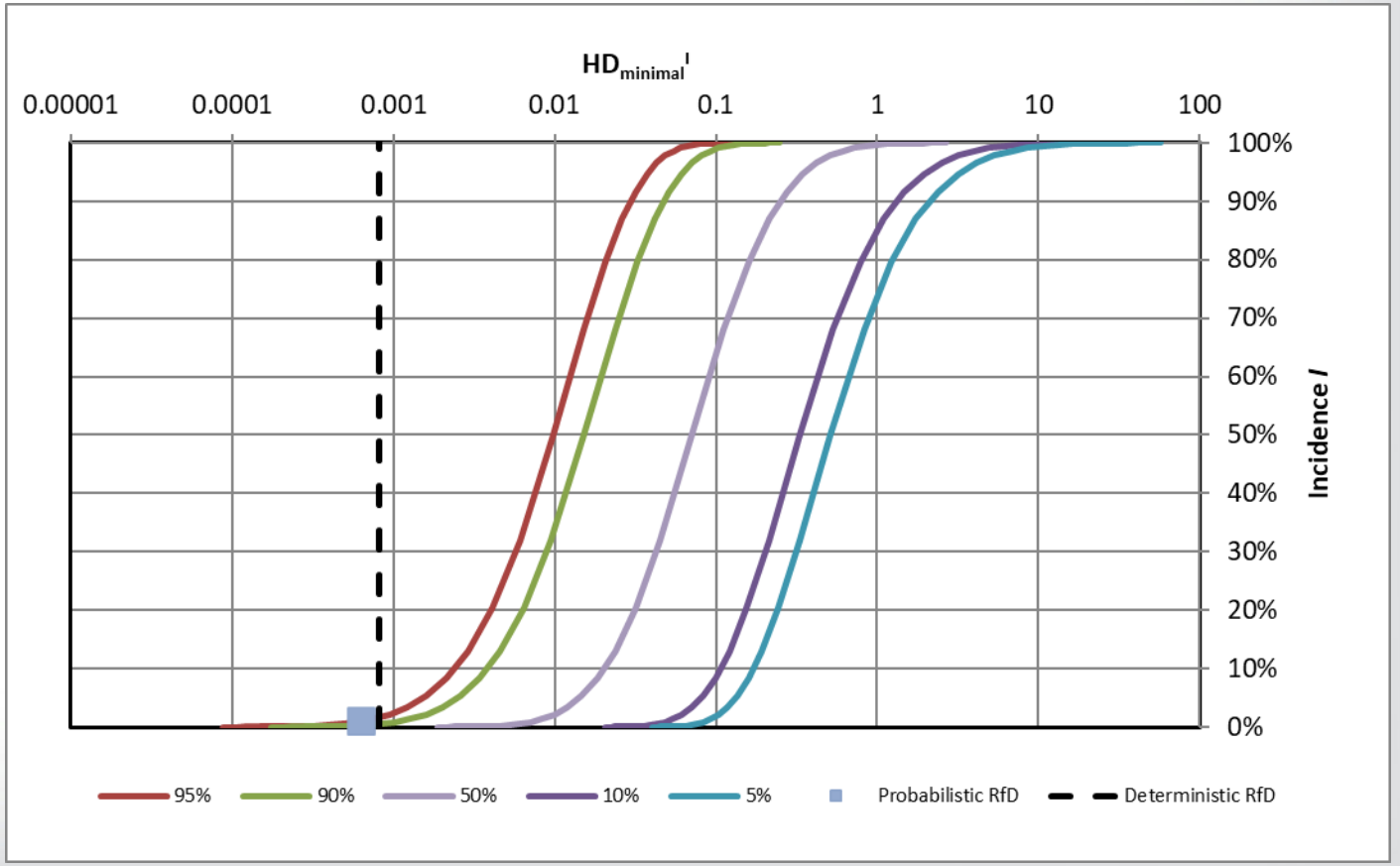
APROBA Analysis	POD Distribution	Duration AF Distribution	$HD_{minimal}^{01}$	Confidence Range (UCL/LCL)
NOAEL - APROBA default	0.082 - 0.246	0.5 - 8.0	6.3×10^{-4} - 8.6×10^{-2}	137
NOAEL - Narrow	0.082 - 0.246	1.0 - 4.0	8.3×10^{-4} - 6.3×10^{-2}	73
NOAEL - None	0.082 - 0.246	1.0 - 1.0	19.2×10^{-4} -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

[a]BMA = 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 = BMR of 5% 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

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