Quantifying Uncertainty in Dose

From the perspective of a person who evaluates uncertainty in environmental pathway models

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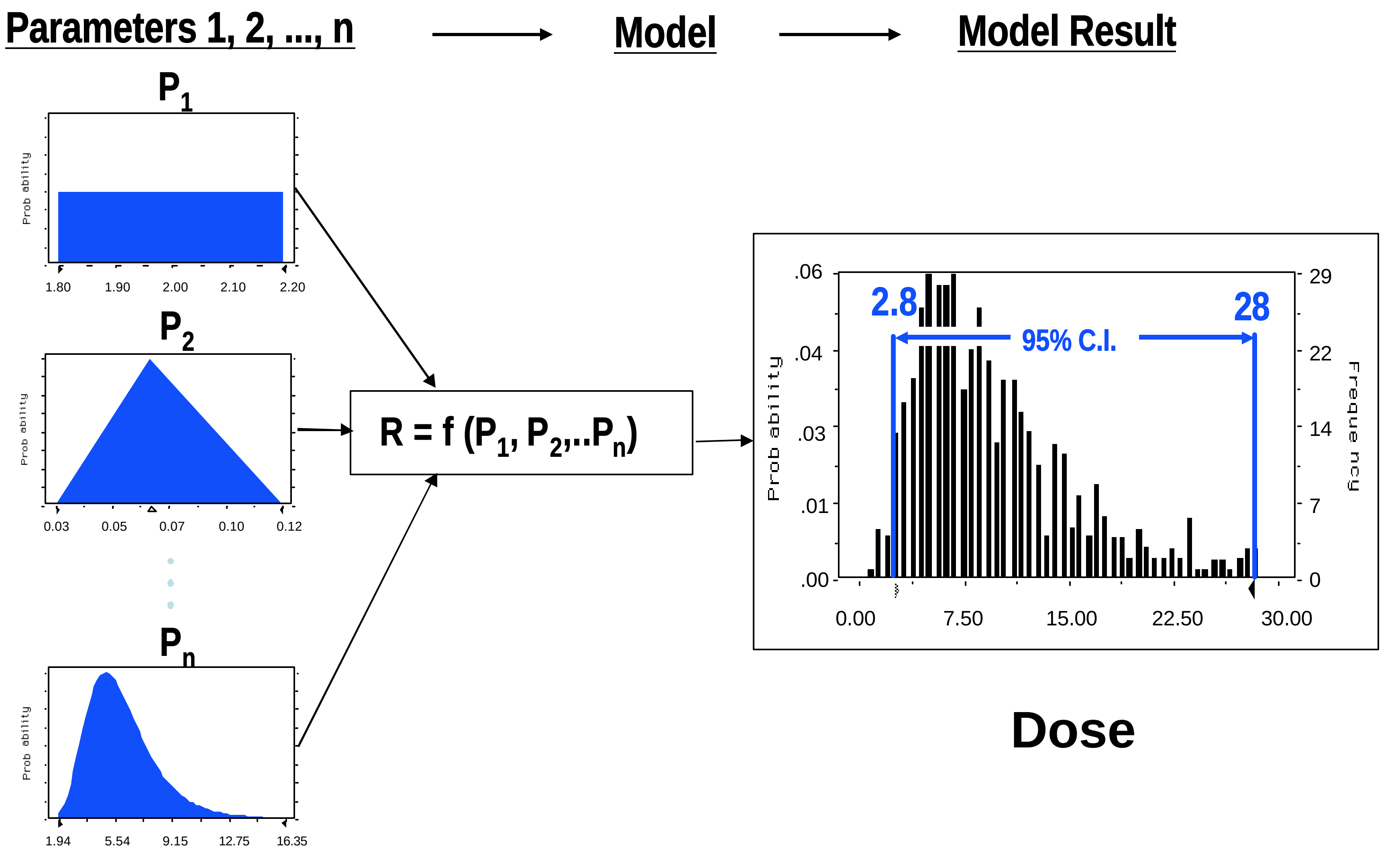
Let’s start with an example problem

- Dose reconstruction for an accident decades ago in which a short-term release occurred of a short-lived radionuclide.
- There are no environmental measurements
- Meteorological dispersion must be inferred from present-day information
  - 90% chance the wind blew to the north
  - Excess disease seen in the south
- What do we conclude?

History of Uncertainty Analysis in Dose Reconstruction

- **Quantification of uncertainty in environmental pathway models**
  - First efforts began more than 30 years ago
  - Algebraic solutions used for multiplicative and additive terms in equations
  - Monte Carlo simulation
    - with uncertain model parameters described as discrete or continuous probability distributions

Estimating Uncertainty for an Individual



The First Epidemiological Study to Address Uncertainty in Dose Reconstruction

University of Utah Investigation of Childhood Cohorts Exposed to NTS Fallout

(Stevens et al, 1992, Kerber et al, 1993)

- Dose uncertainties estimated for each individual in the cohort
  - Algebraic solutions used for equations described by products and summations,
  - Monte Carlo used for some model components
  - Dose per person given as a GM and GSD from which an arithmetic mean was obtained.

The First Epidemiological Study to Address Uncertainty in Dose Reconstruction for Every Individual in the Cohort

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University of Utah Investigation of Childhood Cohorts Exposed to NTS Fallout

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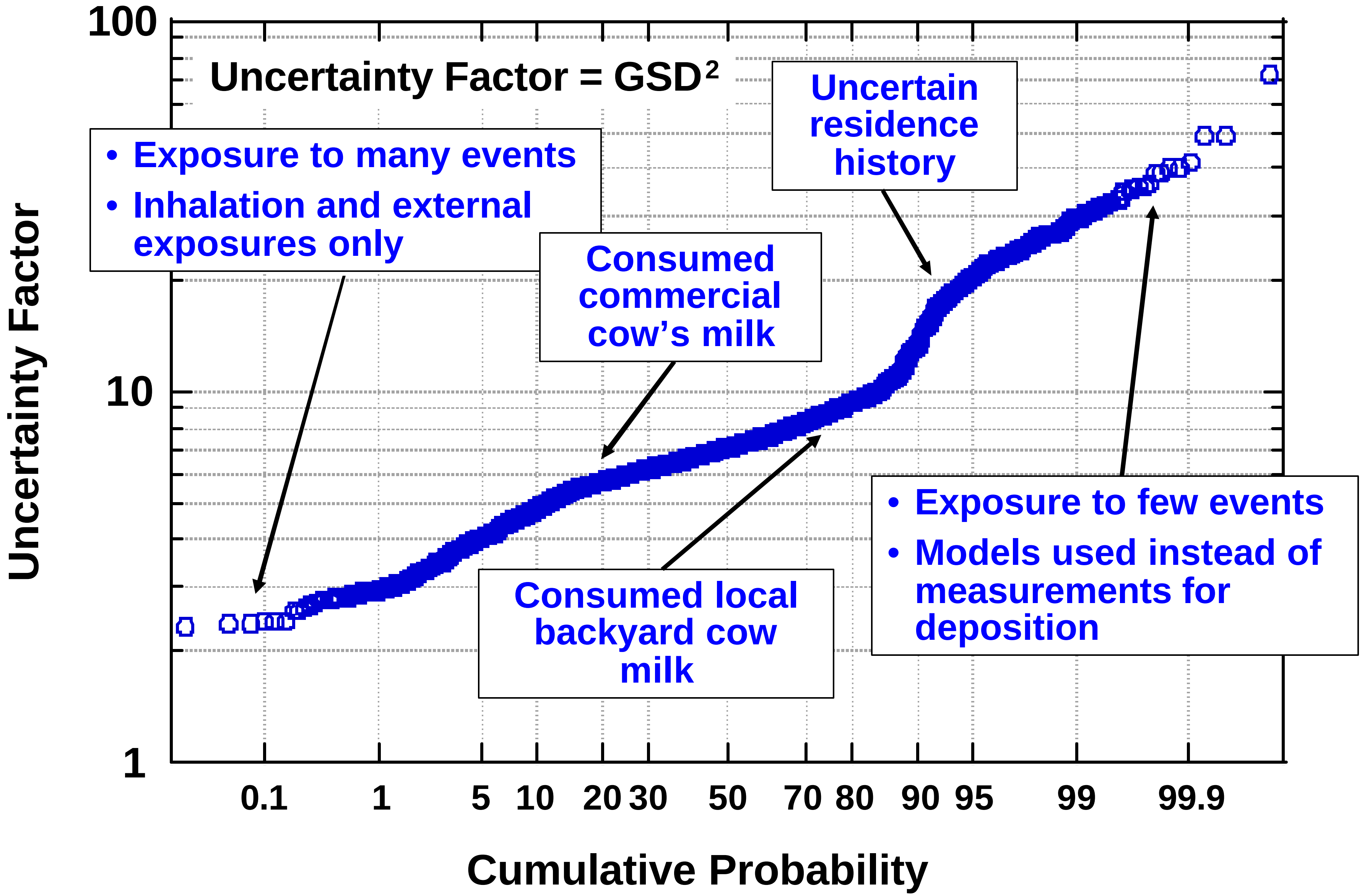
- Primary dose response based on arithmetic mean dose for each individual
  - Initial analysis of dose uncertainty treated all uncertainty as classical measurement error
- Mixtures of classical, Berkson and shared uncertainties considered in more recent work
  - (Malick et al 2004, Lyon et al 2006, and Li et al., 2007)

Uncertainty Factors for NTS Cohort



Hanford Thyroid Disease Study was the First to Use a Full Monte Carlo-Based Uncertainty Analysis of Dose

(Davis et al., 2002, 2004)

- The median individual dose used for primary dose-response analysis
- Amount of dose uncertainty per person somewhat less than for NTS cohort
- Analysis of dose response assumed dose uncertainty as 100% Berkson error
  - Evaluation of varying degrees of potential bias in model parameters not evident

Estimating Dose Uncertainty for an Epidemiological Cohort

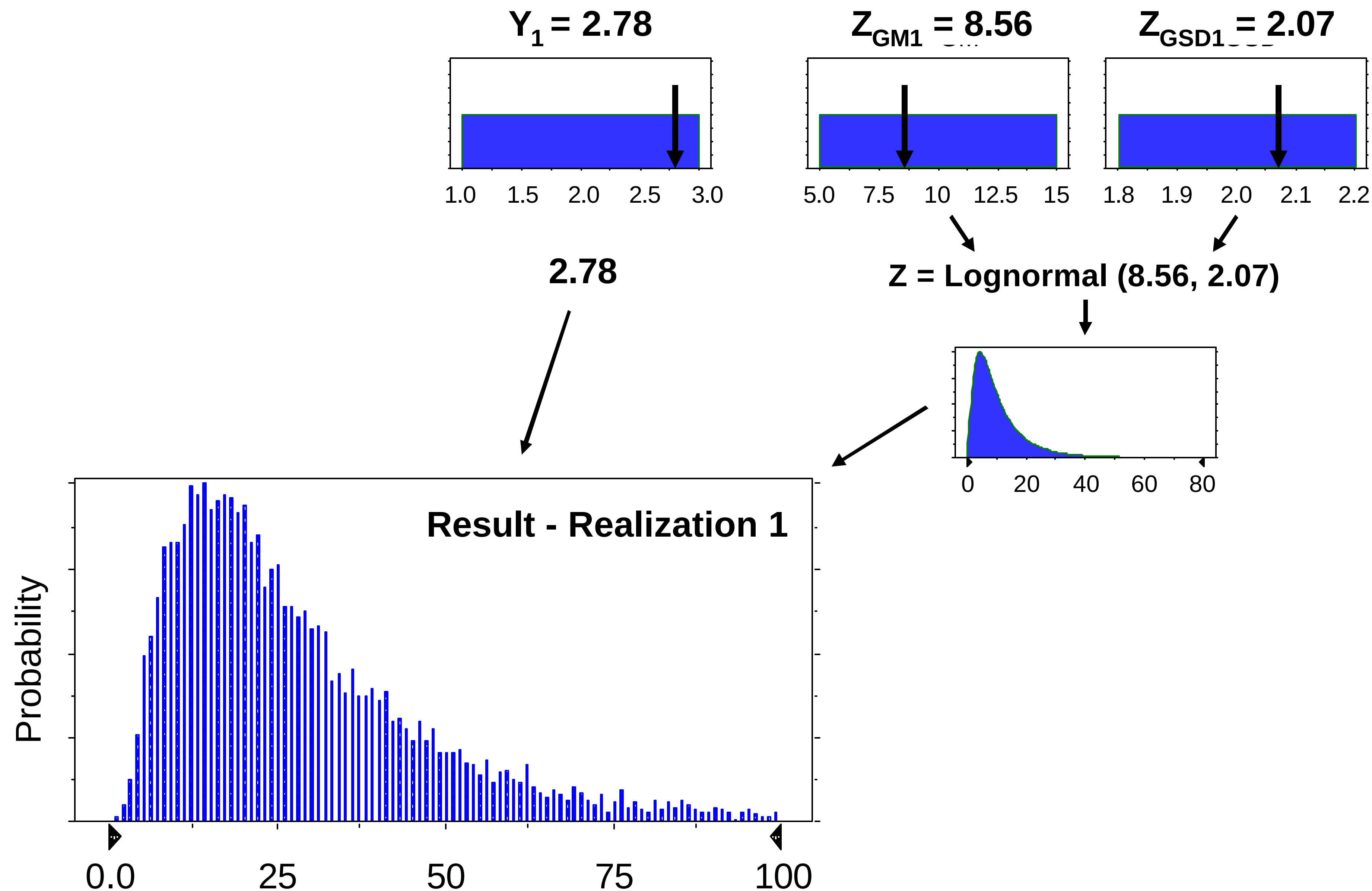
- Stochastic variability of true dose among individuals should be separated from lack of knowledge about true but unknown fixed quantities
- Individuals within and across subgroups in the cohort may be affected by potential bias in model parameters
  - Examples: Amount released, Wind direction, GM and GSD of milk transfer factor

Separation of random variability of true exposure and dose from quantities that are fixed (true) but unknown

- **Requires a 2-Dimensional Monte Carlo Approach**
  - First described in the1980's
  - The terms "Type A" and "Type B" uncertainty introduced

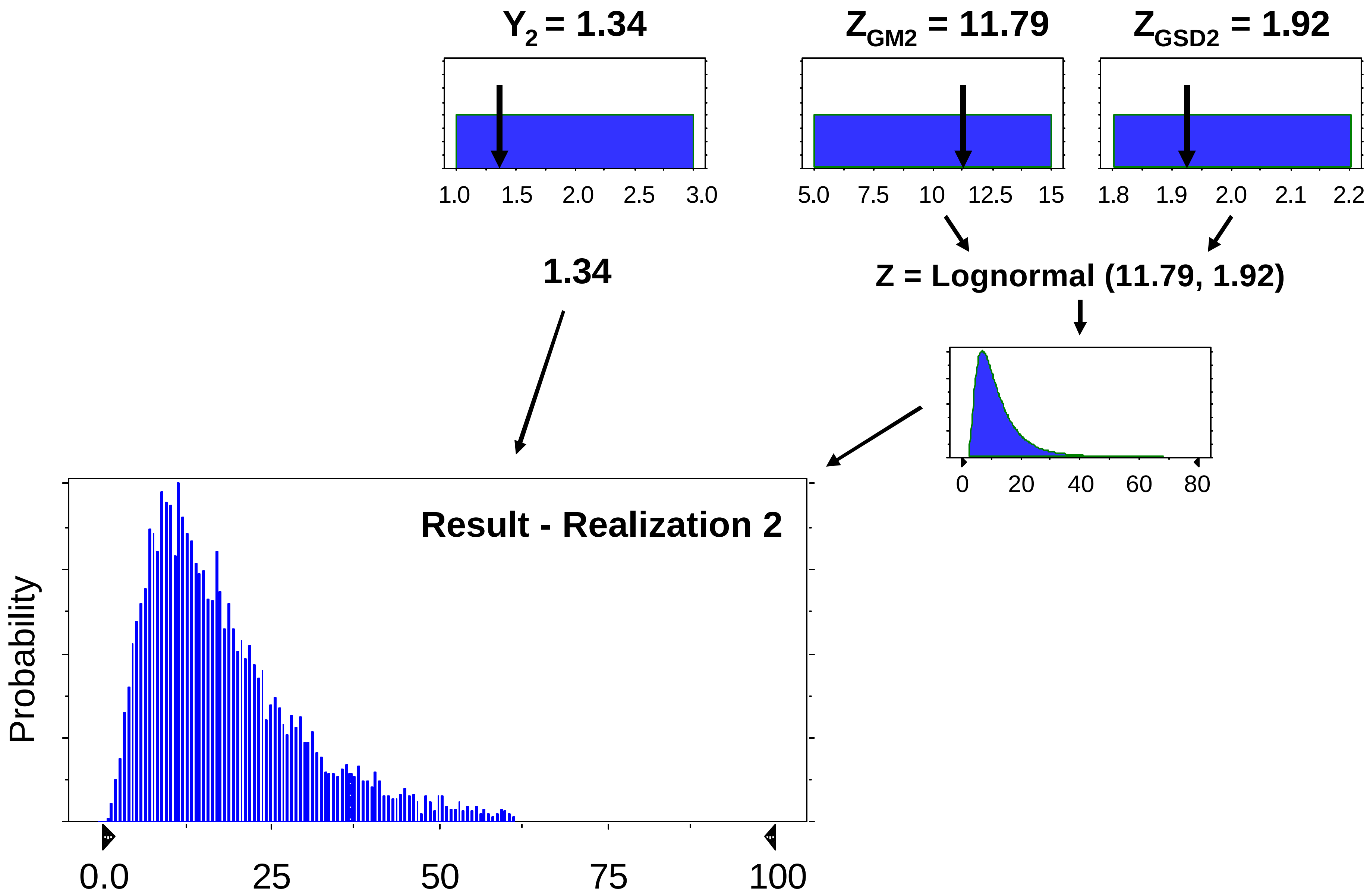
    (IAEA Safety Series No. 100, 1989)

Result = Y × Z



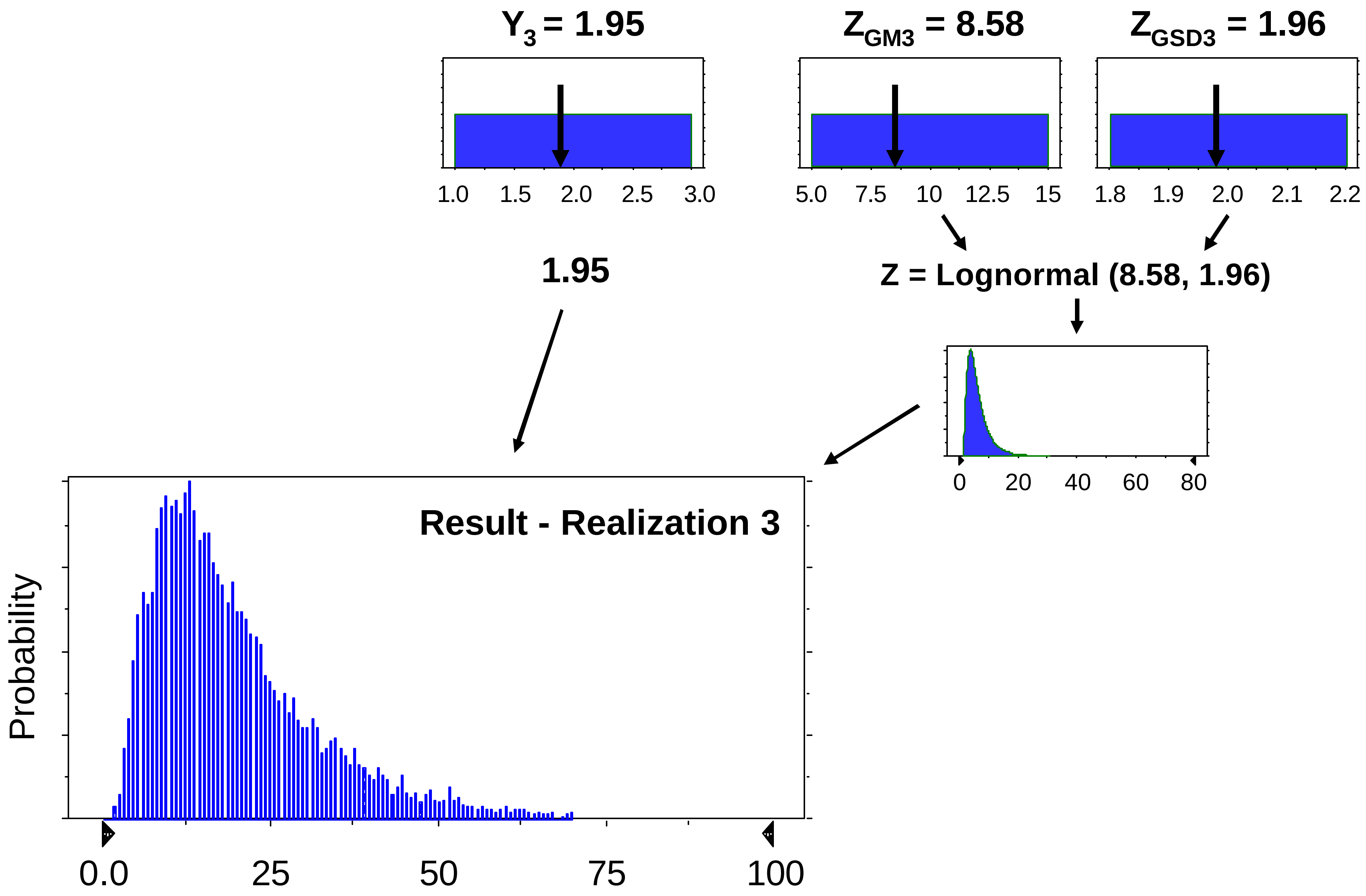
Y1 = 2.78
ZGM1 = 8.56
ZGSD1 = 2.07
1.0 1.5 2.0 2.5 3.0
5.0 7.5 10 12.5 15
1.8 1.9 2.0 2.1 2.2
2.78
Z = Lognormal (8.56, 2.07)
0 20 40 60 80
Result - Realization 1
Probability
0.0 25 50 75 100

Result = Y × Z



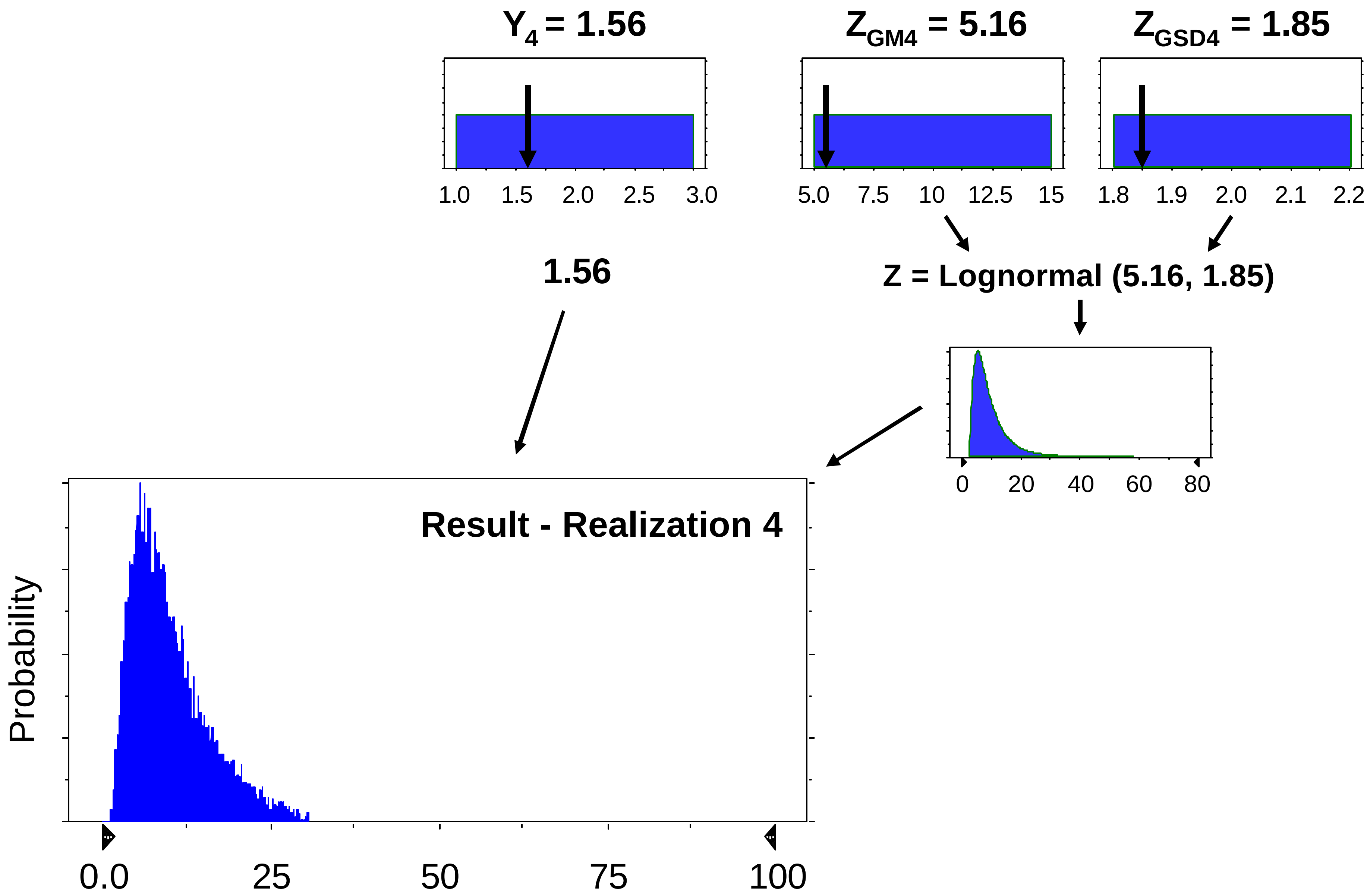
Y2 = 1.34
1.0 1.5 2.0 2.5 3.0
ZGM2 = 11.79
5.0 7.5 10 12.5 15
ZGSD2 = 1.92
1.8 1.9 2.0 2.1 2.2
1.34
Z = Lognormal (11.79, 1.92)
0 20 40 60 80
Result - Realization 2
Probability
0.0 25 50 75 100

Result = Y × Z

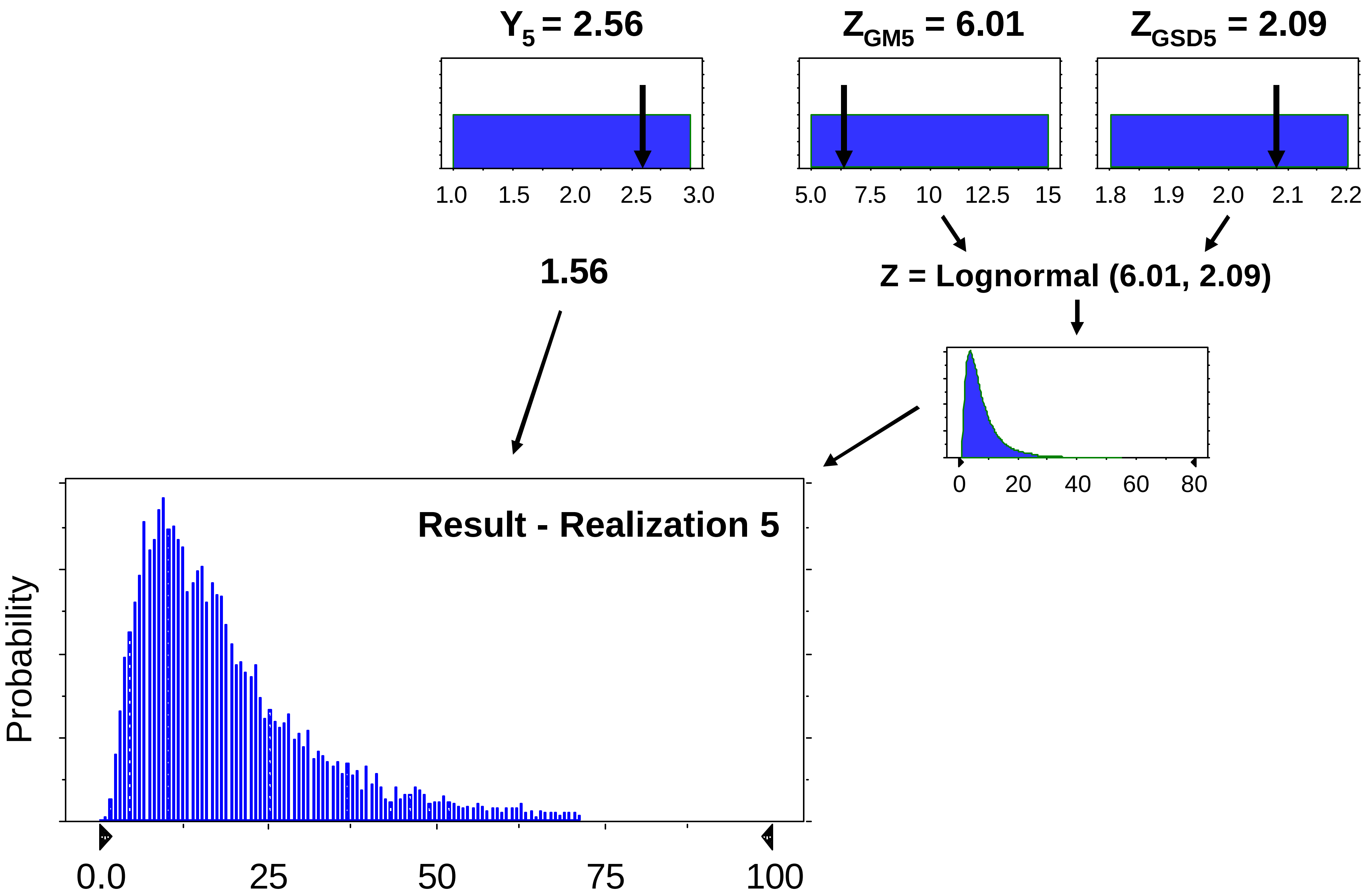


Y_3 = 1.95
Z_{GM3} = 8.58
Z_{GSD3} = 1.96
1.0 1.5 2.0 2.5 3.0
5.0 7.5 10 12.5 15
1.8 1.9 2.0 2.1 2.2
1.95
Z = Lognormal (8.58, 1.96)
0 20 40 60 80
Result - Realization 3
Probability
0.0 25 50 75 100

$$\text{Result} = Y \times Z$$

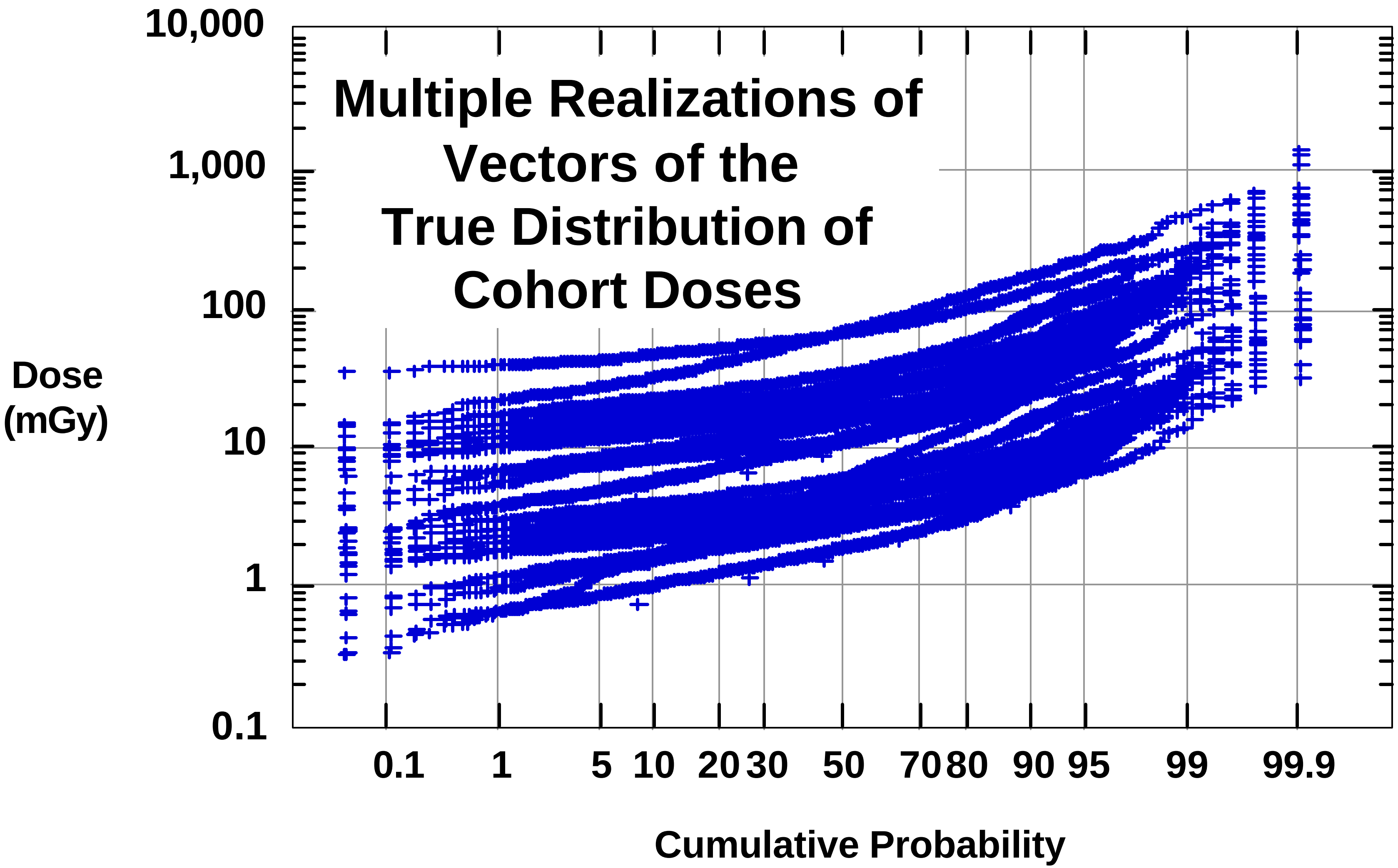


Result = Y × Z

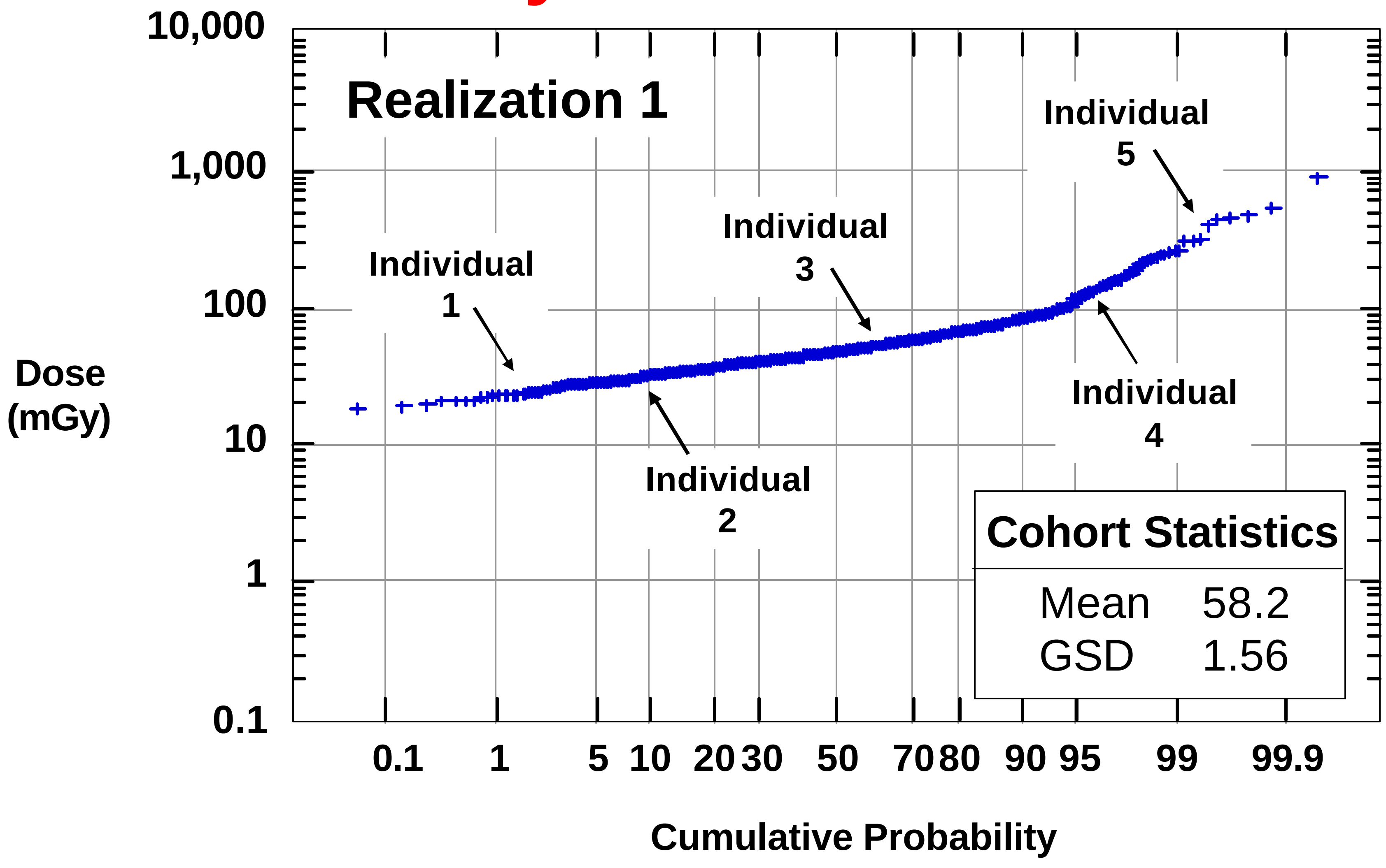


Y_5 = 2.56
1.0 1.5 2.0 2.5 3.0
Z_{GM5} = 6.01
5.0 7.5 10 12.5 15
Z_{GSD5} = 2.09
1.8 1.9 2.0 2.1 2.2
1.56
Z = Lognormal (6.01, 2.09)
0 20 40 60 80
Result - Realization 5
Probability
0.0 25 50 75 100

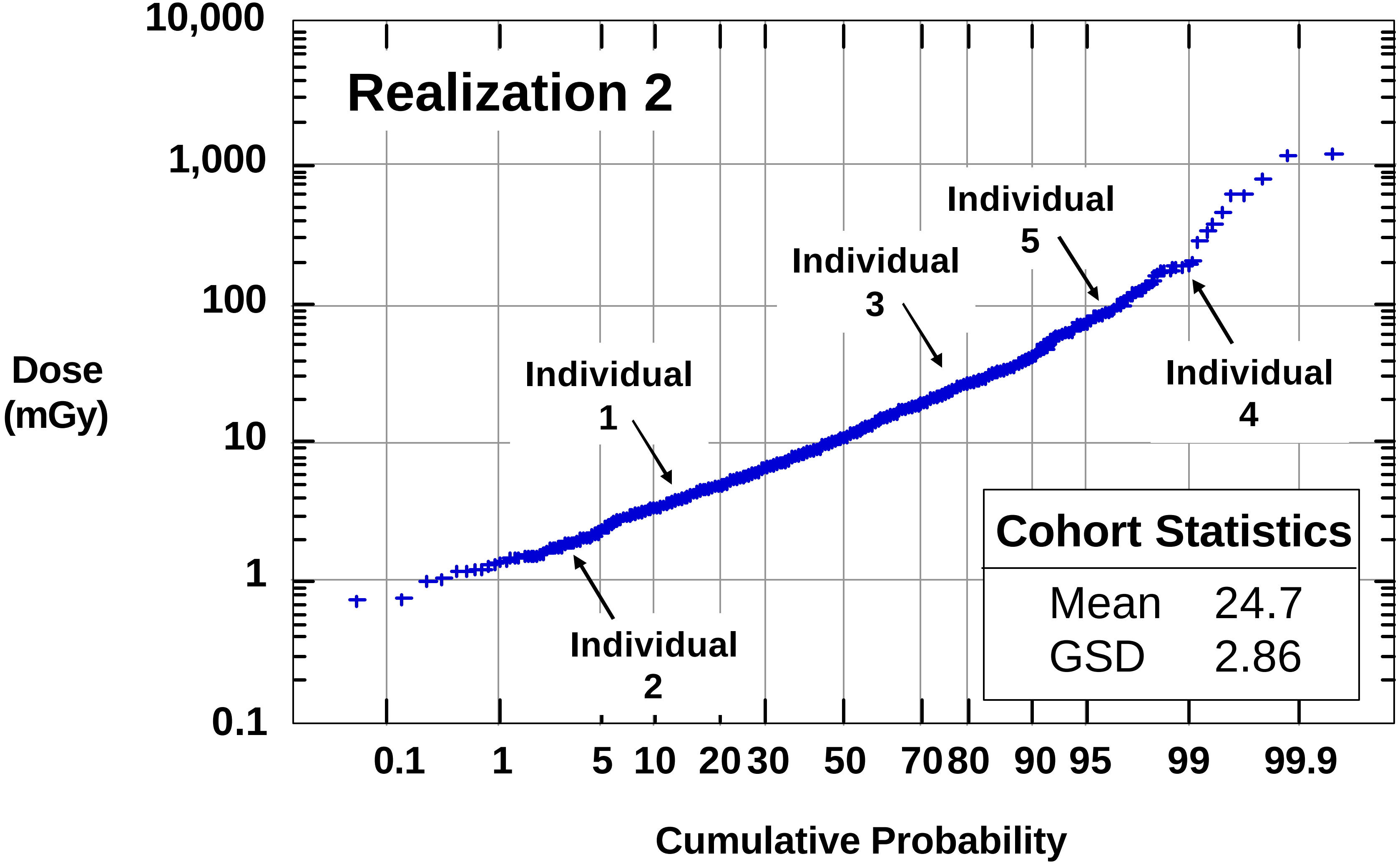
A 2-D Monte Carlo dose reconstruction for a cohort



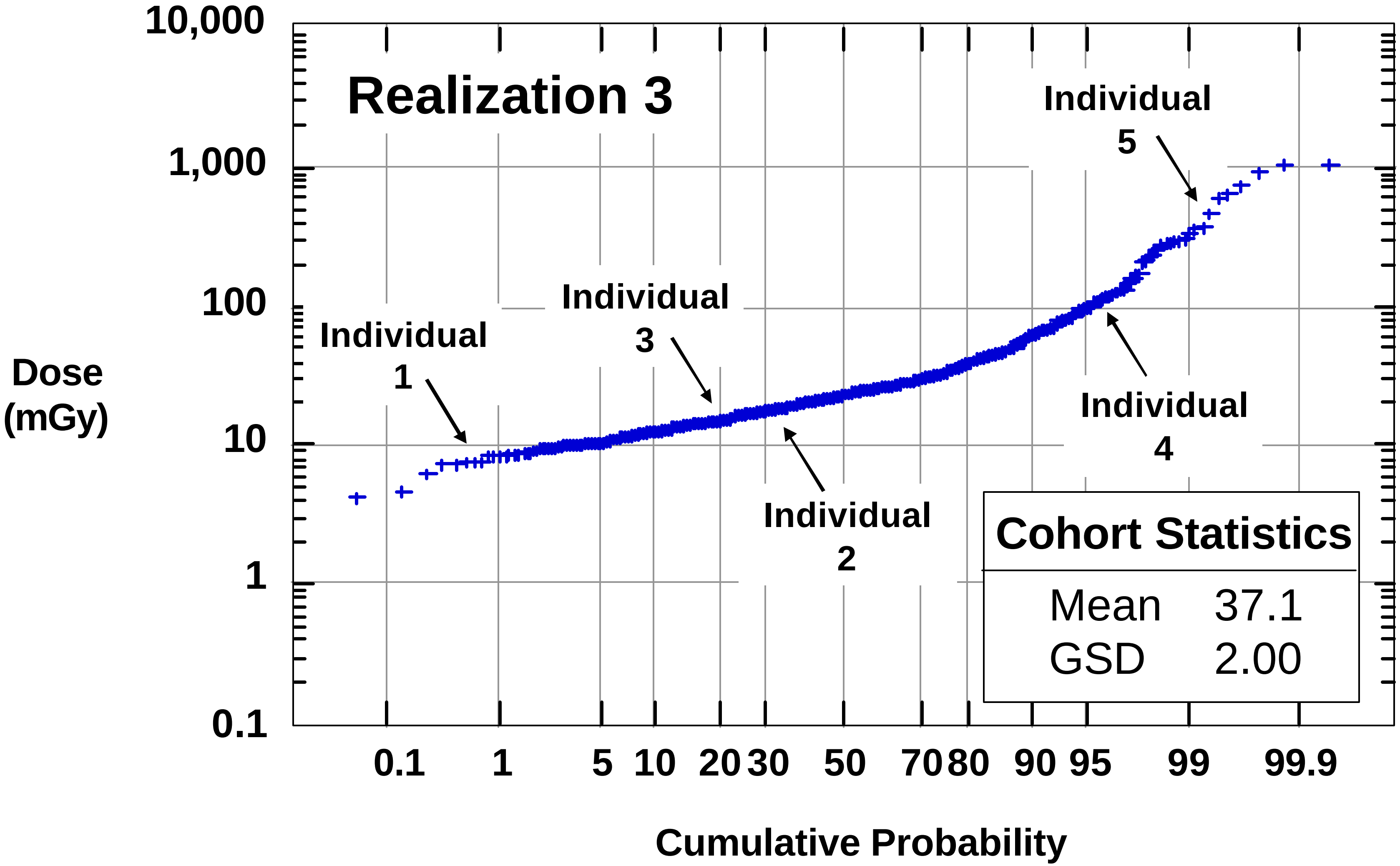
An example of a single realization from a 2-D Monte Carlo uncertainty analysis for a cohort



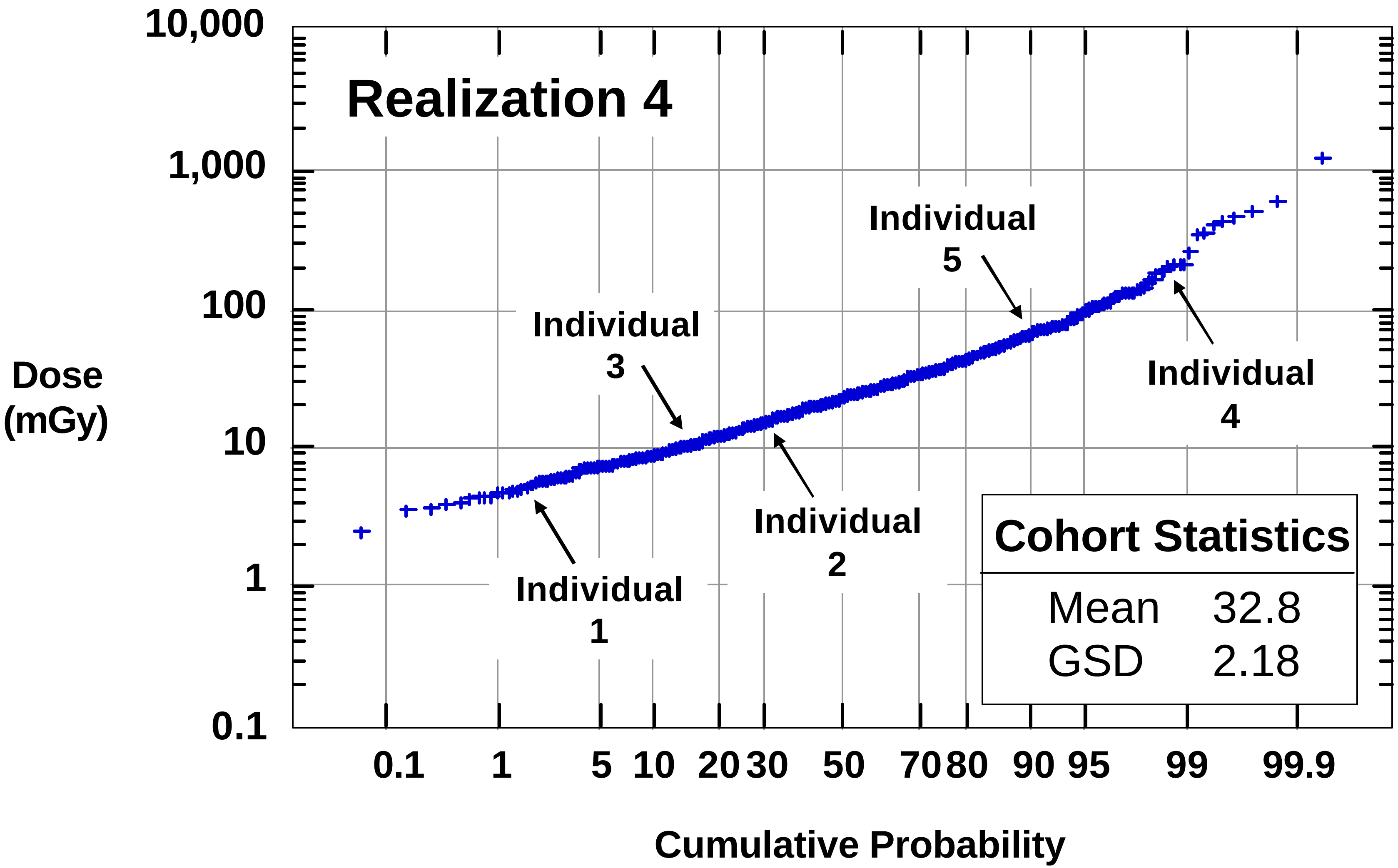
An example of a 2-D Monte Carlo uncertainty analysis for a cohort



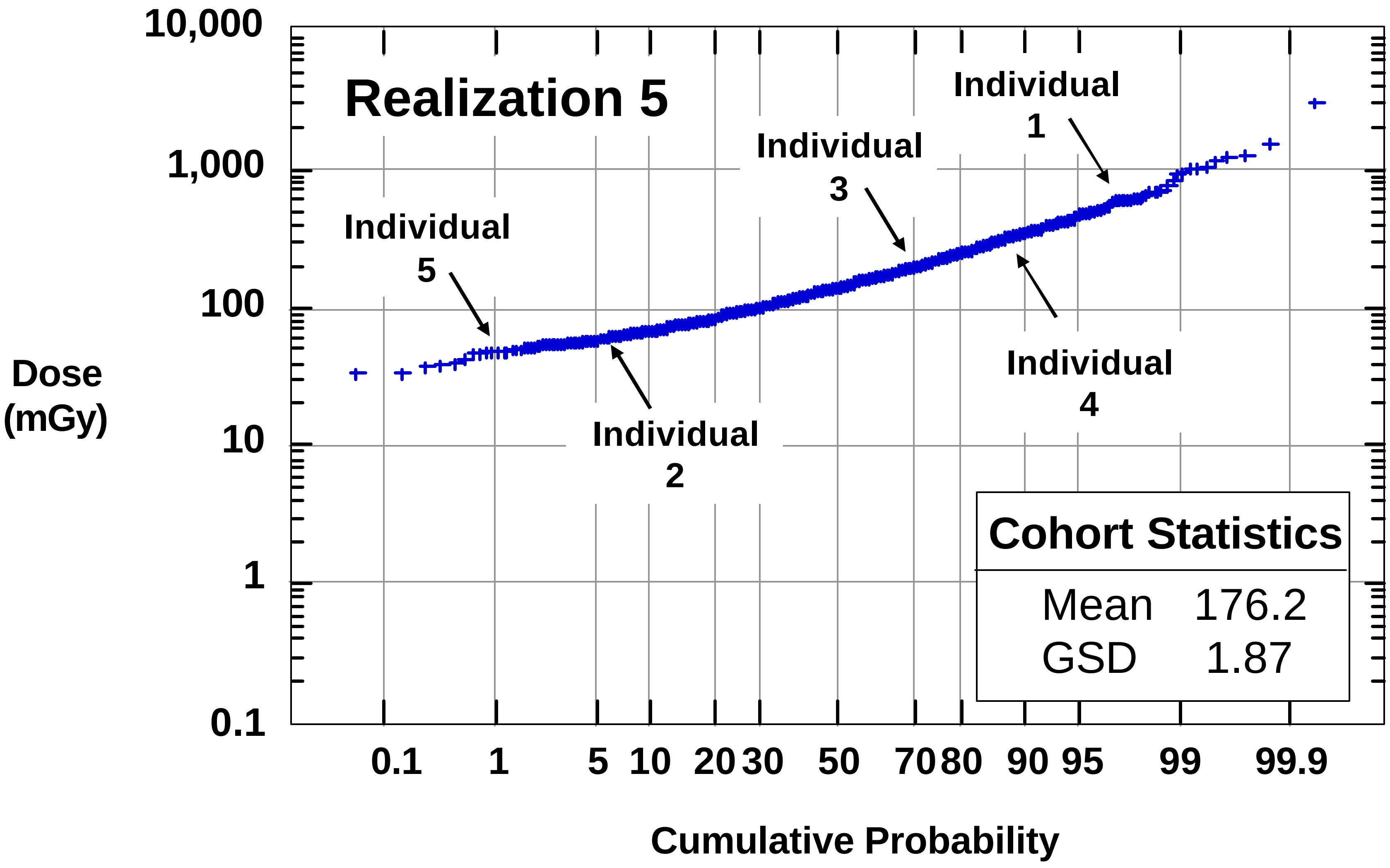
An example of a 2-D Monte Carlo uncertainty analysis for a cohort



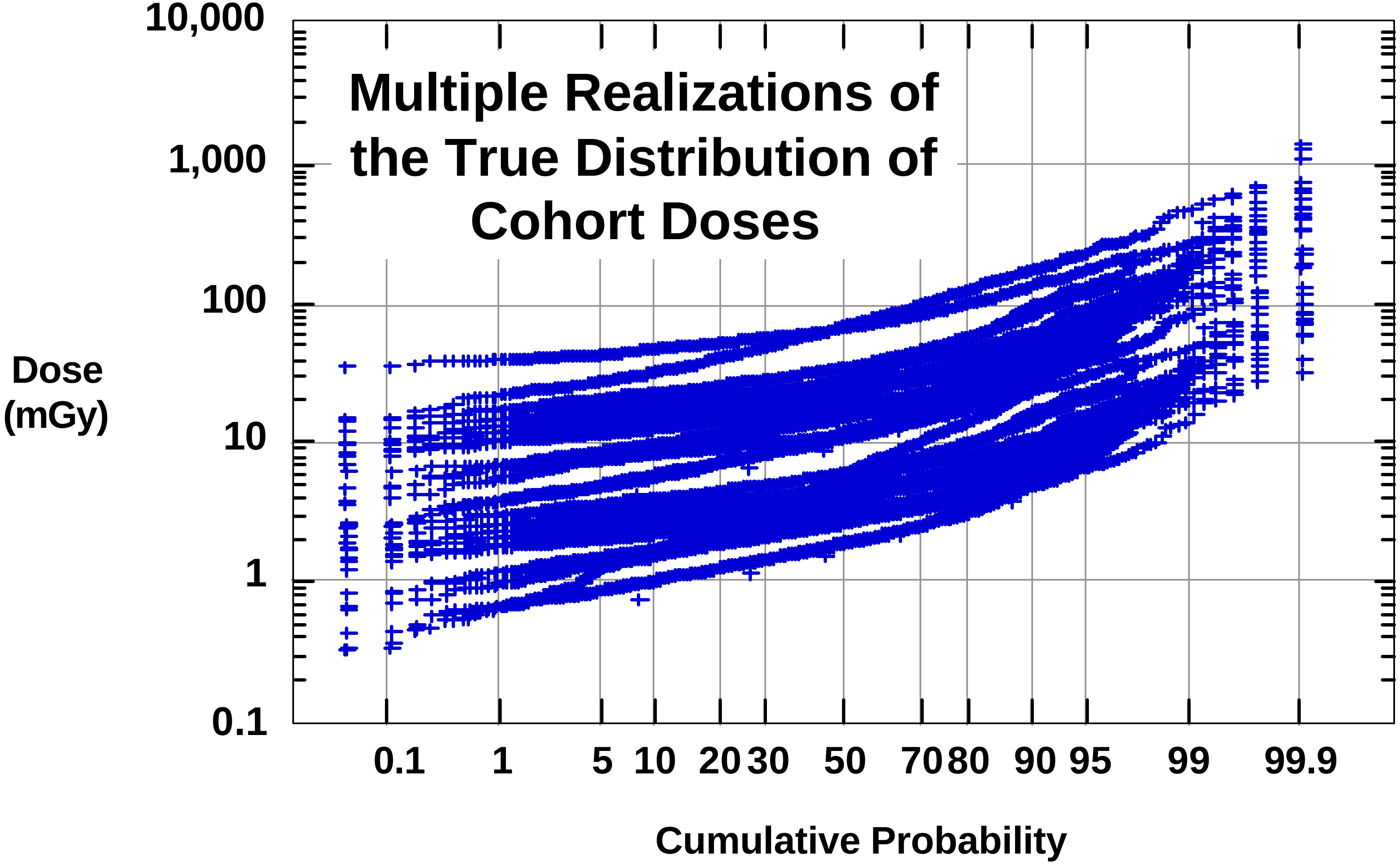
An example of a 2-D Monte Carlo uncertainty analysis for a cohort



An example of a 2-D Monte Carlo uncertainty analysis for a cohort



What do Epidemiologists do with results from a 2-D Monte Carlo Simulation?



What do Epidemiologists do with output from a 2-D Monte Carlo Simulation?

- Use mean dose as a surrogate for the true dose and ignore uncertainty (regression calibration)?
- Assign equal weight to each alternative dose response and average?
- Obtain the likelihood of each realization of dose response and average?
- Perform more complex analyses as in Li et al (2007)?
  - To account for mixtures of classical and Berkson errors
  - To account for shared uncertainties due to possible bias in parameter values and model structure

Important considerations when evaluating a 2-D Monte Carlo Dose Reconstruction

- All realizations of dose vectors may be “wrong”, hopefully some will be “less wrong” than others
- When there is the potential for a high degree of systematic error (bias) shared by subgroups of the cohort
  - Only a few alternative realizations of dose vectors might approximate the true distribution of individual doses
- Under these conditions, it is not recommended
  - To use the mean dose as a surrogate for the true dose
  - To give equal weight to each alternative dose response

Recommendation

- Perform a dose response analysis
  - On each realization of the cohort distribution of doses
- Evaluate and weight each alternative dose response for degrees of plausibility
  - Use goodness of fit to disease outcomes
  - Perform investigations to further justify why some realizations of dose and dose response are more plausible than others
- If an unbiased mean dose per person is desired,
  - Produce alternative vectors of possibly unbiased mean doses

Don’t overlook QA/QC of the dose reconstruction model and input data

- Complex computer codes and data bases frequently contain errors
- Consider redundant computational platforms programmed independently
  - Compare intermediate results and dose estimates
  - Compare estimates of uncertainty
  - Resolve discrepancies

“The biggest problems are caused by things you think you know for sure, that just ain’t so”

Conclusions

- When dose uncertainties are high and complex, be skeptical of dose -response analyses that conclude:
  - "Dose uncertainties did not affect the dose-response"
- Use 2-D Monte Carlo to separate random variability from lack of knowledge about true fixed quantities
  - Weight each realization of a cohort distribution of true doses by degrees of plausibility
  - Dosimetrists should participate in this evaluation
- Resist averaging doses across realizations
- Explicit evaluation of each realization of a possibly true vector of cohort doses will identify
  - situations associated with low statistical power
  - situations that give an improved fit to health outcomes