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AHETF & AEATF II

Exposure Monitoring Programs & Generic Databases

Concepts, Objectives, and Sampling Issues

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Outline

- Important definitions & concepts
- Objectives of the monitoring programs
- Limitations
- Currently proposed designs
- Probability sampling issue

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Handler-Day Exposure

The exposure that a chemical handler would incur during a workday when performing tasks associated with a particular occupational scenario.

$$= \mathcal{E}x(\, a, C\,)$$

Active ingredient handled

Set of handling conditions (includes the particular handler)

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3 Categories of Handler-Days Relevant to this Program

Natural — *A handler-day that actually occurs in practice under conditions not simulated, scripted, or otherwise controlled by the experimenter*

Synthetic — *A 'non-natural' handler-day. Some (but not necessarily all) conditions have been simulated, scripted, or controlled by the experimenter*

Surrogate — *A handler-day that can be used as a 'substitute for' other handler-days. Surrogate handler-days could be either natural or synthetic.*

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Definition:

Monitoring Event (ME)

Monitoring Unit (MU)

The specific monitoring activities conducted by researchers to obtain exposure measurements for a <u>single</u> handler-day (natural or synthetic).

Includes all conditions (including subject) associated with an experimentally determined handler-day exposure.

Synonymous

- *AHETF tends to use MU*
- *AEATF tends to use ME*

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Generic Exposure Principle

Under the same 'handling' conditions, handler-day exposure does not depend on the particular active ingredient

$$\mathcal{E}x(\text{ a, C }) \quad = \quad \mathcal{E}x(\text{ b, C })$$

Same Conditions

Thus, exposure data from one chemical can serve as a surrogate for predicting exposure to other chemicals

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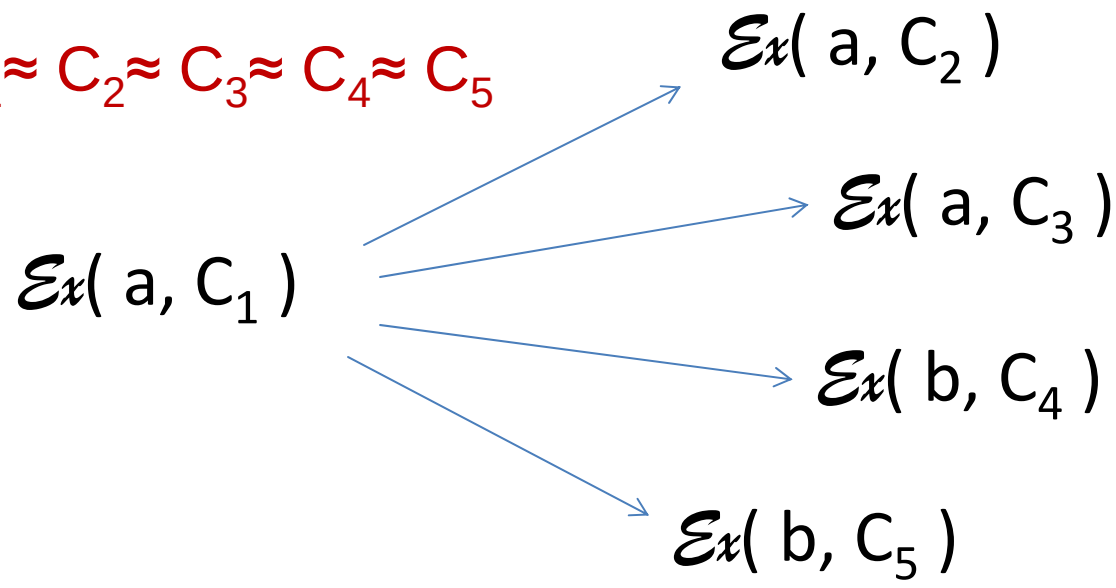
Prediction is also Feasible when Handling Conditions are Sufficiently Similar

When $C_1 \approx C_2 \approx C_3 \approx C_4 \approx C_5$



This might be sometimes be a reasonable assumption based on expert opinion

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An Important Component of 'Handling Conditions':

Amount of Active Ingredient Handled (AaiH)

AaiH is any single measure that quantifies the expected degree of worker contact with active ingredient

The Most Common AaiH Measure:

Total amount of a.i. 'used' during a workday
e.g., (total volume sprayed) x (a.i. concentration)

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But other Measures of AaiH can sometimes be more Reasonable

e.g., Closed System Mixing/Loading:

(# times equipment 'touched') x (concentration of a.i.)

e.g., Continuous, repetitive tasks such as mopping & wiping:

(duration of task) x (concentration of a.i.)

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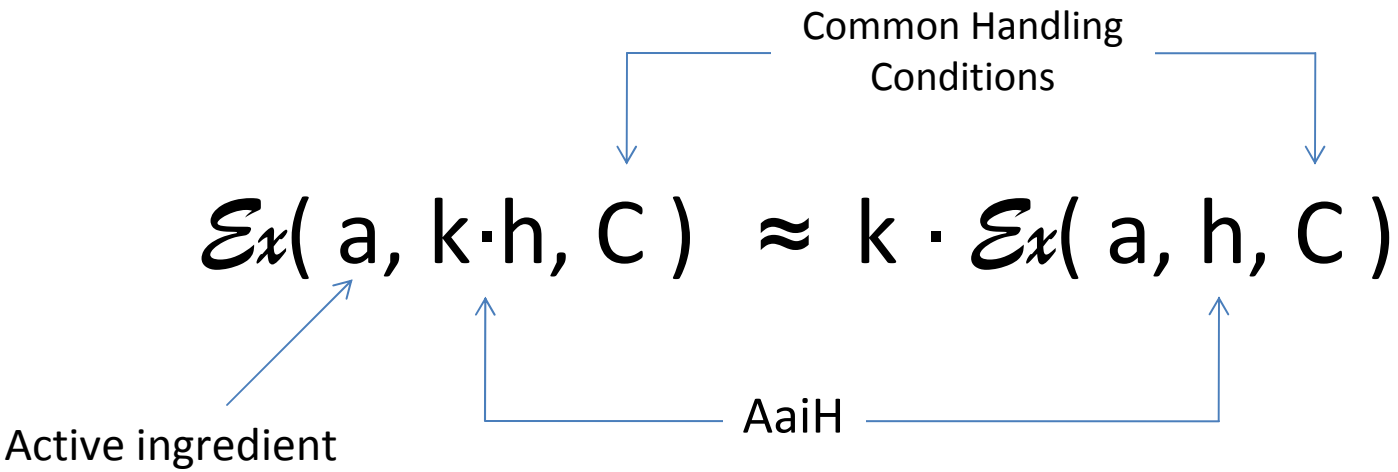
A Common and very Useful AaiH Assumption: 'Proportionality'



e.g., Doubling AaiH Implies Doubling Exposure

Approximate proportionality is reasonable when an appropriate AaiH measure is used

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Proportionality Provides a Broader Class of Surrogate Exposures

The predicted exposure for a different a.i. & AaiH level

$$\mathcal{E}x(x, h_x, C)$$

2 Different Surrogate Exposures

$$\left[\frac{\mathcal{E}x(a, h_1, C)}{h_1} \right] \cdot h_x$$

Normalized Exposure to a

$$\left[\frac{\mathcal{E}x(b, h_2, C)}{h_2} \right] \cdot h_x$$

Normalized Exposure to b

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Another Important Component of 'Handling Conditions':

Individual Worker

The physical characteristics and work behavior of each unique 'handler' influences exposure, even if the other conditions are the same

$$\mathcal{E}x(\ a,\ h,\ w_1,\ C\ ) \quad \neq \quad \mathcal{E}x(\ a,\ h,\ w_2,\ C\ )$$

Different Workers

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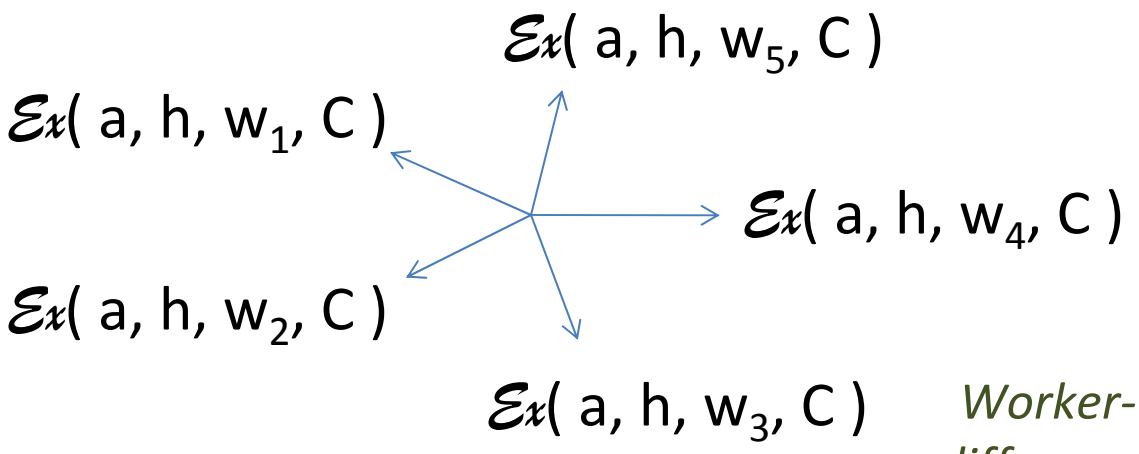
Unlike AaiH, the Aggregate Effect of 'Worker' is Considered Non-Predictive

No simple way to 'transform' one worker's handler-day completely into another's

(Although, partial normalization of exposure by easily measured physical characteristics (e.g., body weight) is sometimes considered)



Worker-worker exposure differences treated as non-predictable 'variation'

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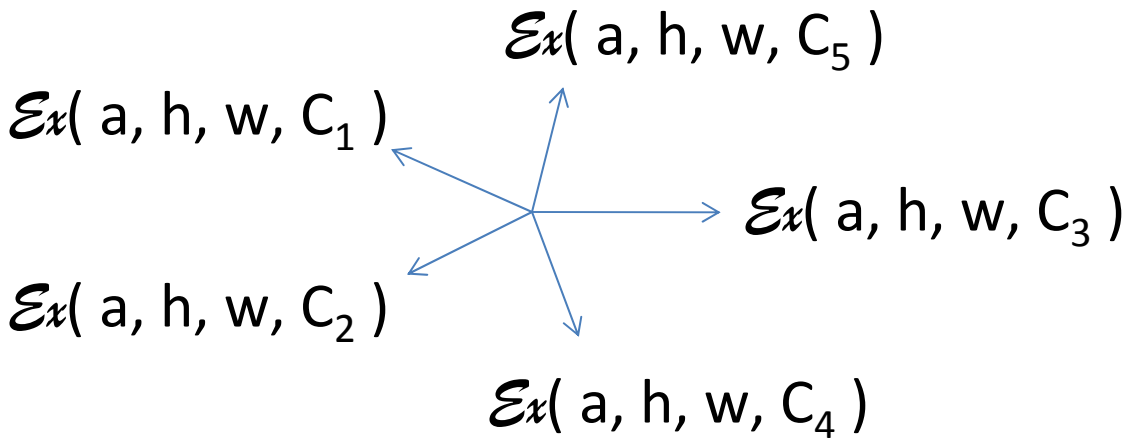
As are Many Other Handling Conditions

e.g., Equipment, location, crop, room type, cleaning surface, environmental conditions, etc.

They obviously impact exposure, but there are no widely accepted relationships that allow them to be used as generic predictors



In general, different 'conditions' also treated as non-predictable 'variation'

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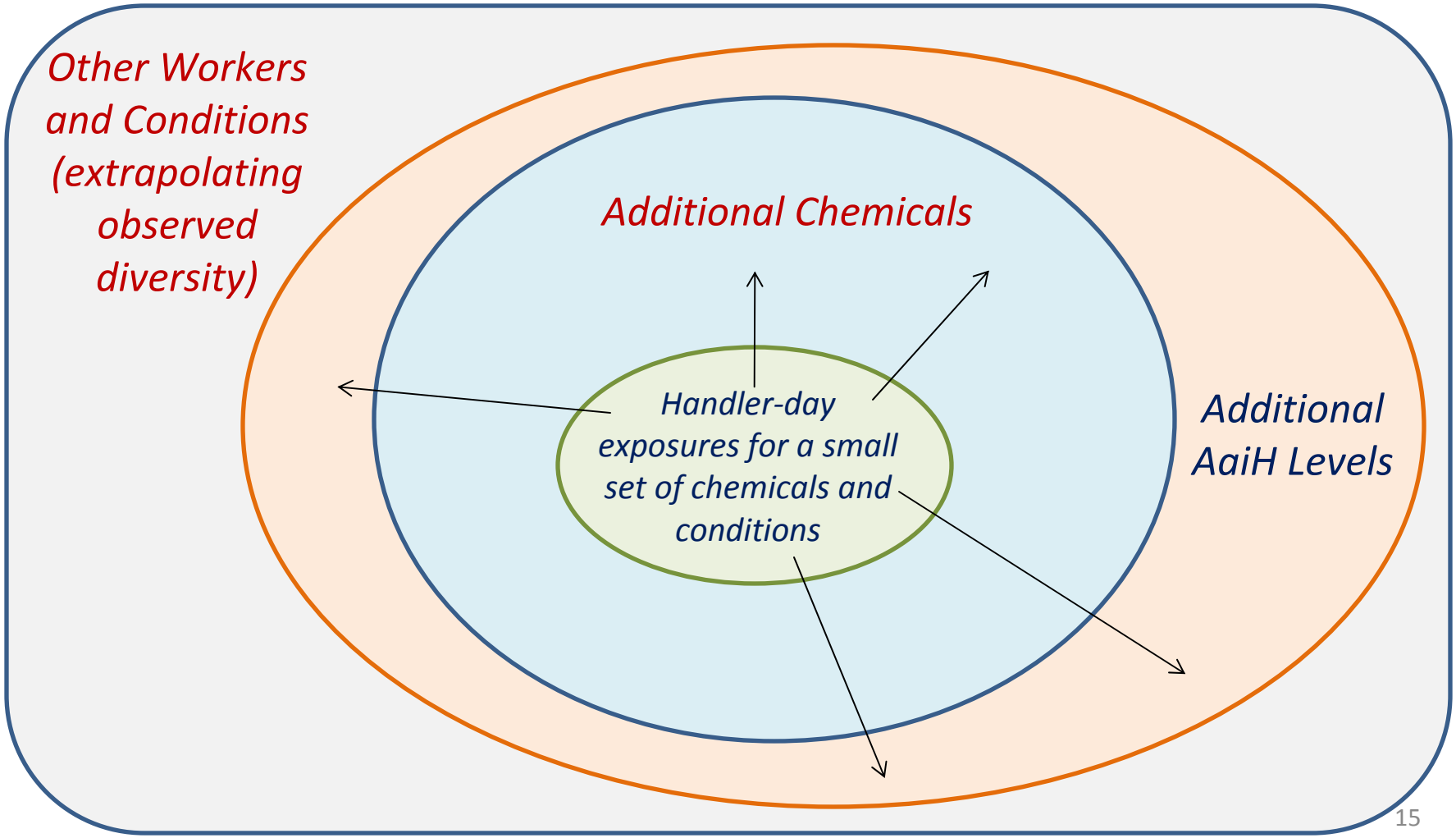
These Concepts make Creation of a Generic Future Exposure Database Feasible



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Goal of Both Programs

- Obtain a database of natural and/or synthetic handler-day monitoring events (MEs) within each of a number of handling scenarios
- Databases are the Objective, not particular analyses of the data
- These MEs will be used (by regulators and others) as surrogate handler-days to characterize future exposures for regulatory purposes

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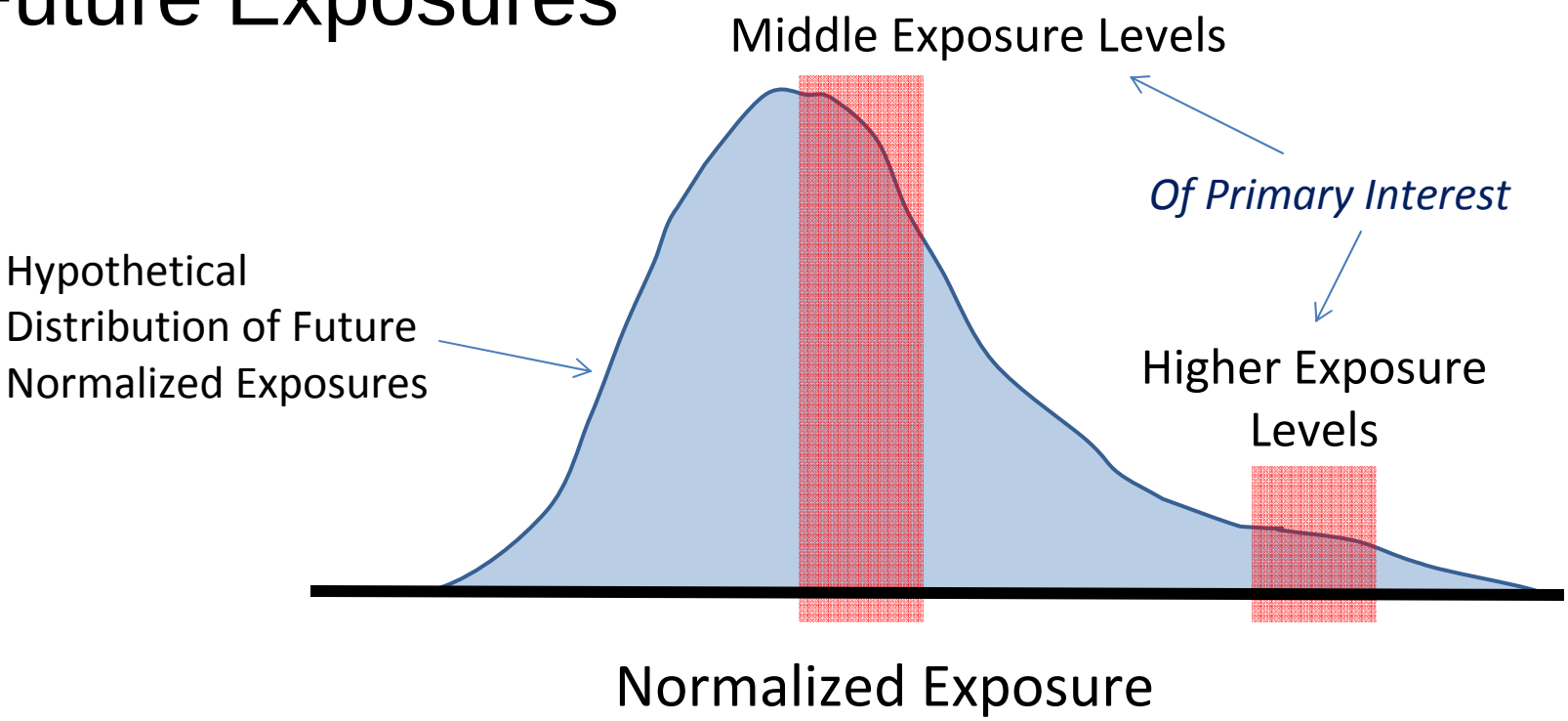
Future Exposures



In principle, this represents an array of potential exposures possible for an arbitrary a.i. with AaiH=1 under this scenario

(If Appropriate AaiH Measure is Used)

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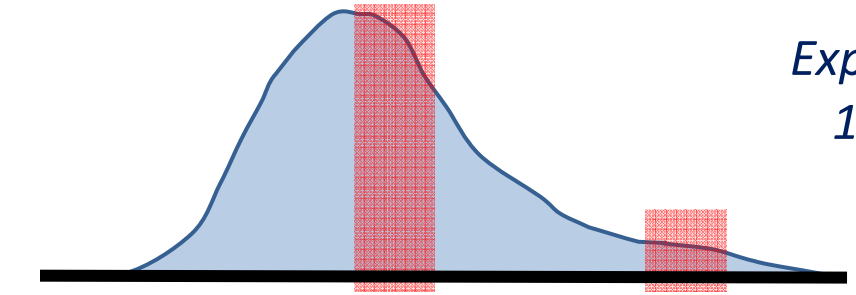
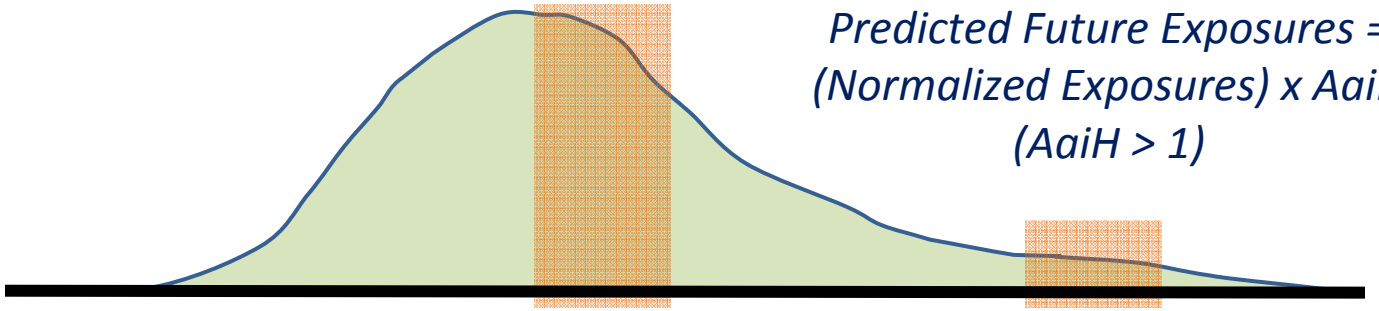
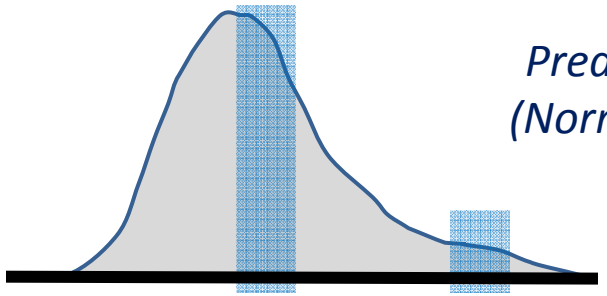
Multiplication of Normalized Exposure by an AaiH of Interest Gives Predicted Future Exposures



Exposures
1)



Predicted Future Exposures =
(Normalized Exposures) x AaiH
(AaiH > 1)



Predicted Future Exposures =
(Normalized Exposures) x AaiH
(AaiH < 1)

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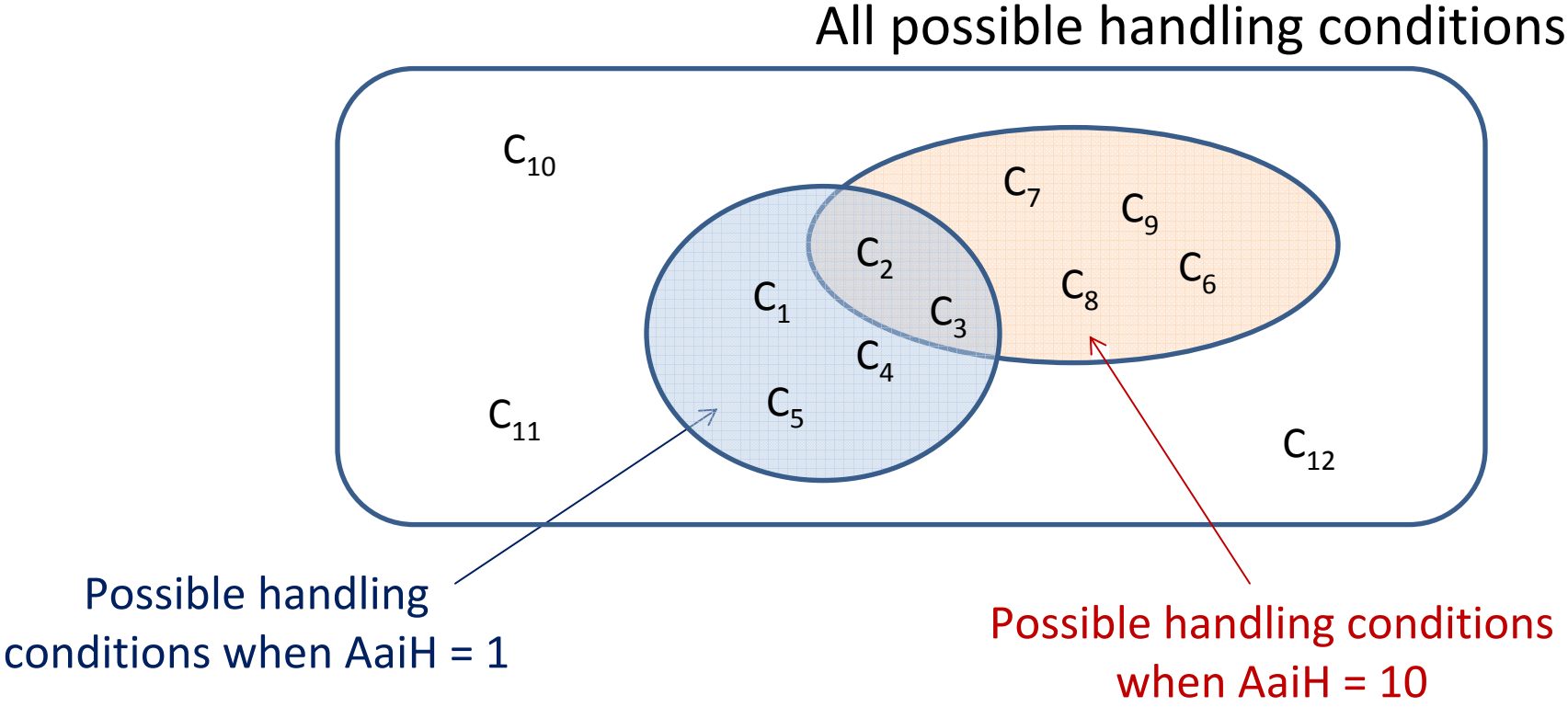
Note: Handling Conditions can still be Associated with AaiH



Therefore, a set of normalized exposures, derived from different levels of AaiH, is likely to be more diverse than exposures with AaiH = 1

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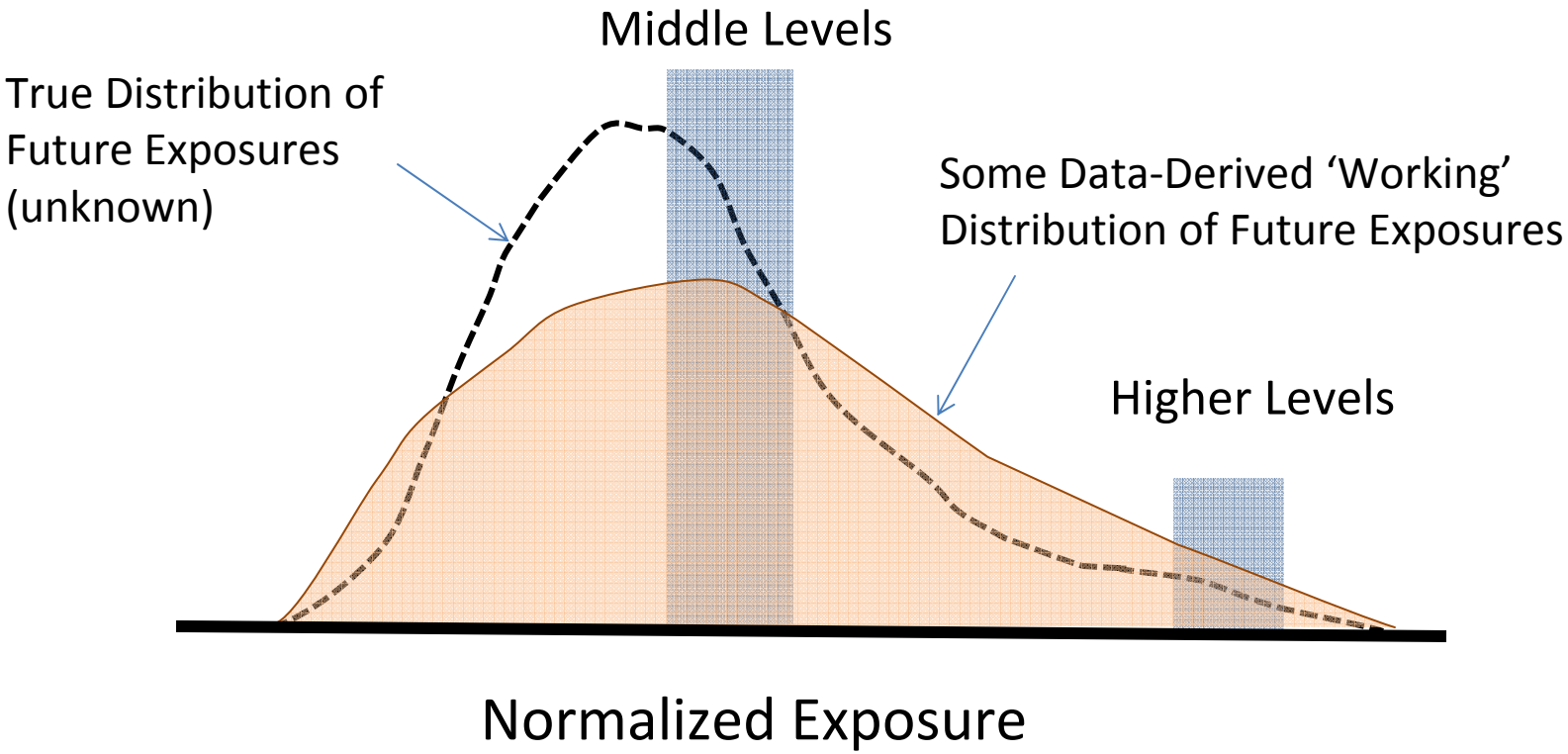
The Actual Distribution of Future Exposures would be Nice but is not Absolutely Necessary

A 'broad swath' across possible exposure values is acceptable if it provides a reasonable indication of middle and extreme exposures



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Program Limitations  & Restrictions

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Resources are Limited

- Limited number of chemicals can be monitored
  AEATF - a single chemical per scenario
- Limited number handler-days can be monitored per scenario
  Mean costs/ME are extremely large
  (AHETF: $35K / ME; AEATF: 30K / ME)
- Number of scenarios is essentially fixed
- Estimated cost of currently proposed program greatly exceeds original task force budget (some members may withdraw)
- Further increases in program cost will likely doom project

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Synthetic Handler Days are Necessary

- Purely natural handler-days for the small number of chemicals (with their associated AaiH levels & conditions) available are not sufficient to span the scenario

- AEATF: Access to actual work environments is not often practical or permissible

- Synthetic handler-days are created to reproduce and diversify conditions that occur in the scenario, albeit not necessarily with the particular surrogate a.i. used.

However, apart from the scripted conditions, subjects do perform tasks as they normally would

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Synthetic Handler Days

AEATF

Experimental work environments created; actual workers perform semi-scripted tasks to simulate a wide array of handler-day conditions

AHETF

Agricultural handlers located that are either handling surrogate chemicals under targeted conditions or are willing to do so

Some MEs may represent natural handler-days. Others are synthetic: partially scripted to induce conditions more typical of non-surrogate chemicals.

All targeted conditions are designed to increase diversity of the 'sample'

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AHETF

Data are Obtained in Clusters

- Monitoring activities must occur during a research visit to a particular geographic location during a fixed time period

- Considerable overhead for each visit, therefore cost effective to obtain multiple MEs per 'visit' (i.e., a cluster of handler-days)

  In the past, each research visit often corresponded to an independent study. Extent typically < 100 miles, < week duration

- Existing data indicate that mean exposures can differ between 'visits'

  This known 'study effect' is caused by many factors that differ in space/time. Some known, many of them unknown. Collecting all handler-days from a single 'cluster' could under estimate the scenario diversity.

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AEATF Data also Obtained in Clusters

- Monitoring activities must occur at a particular building used to synthesize work environments and during specific dates (i.e., a site/period)
- It is cost effective to obtain a cluster of multiple MEs at each site/period
- There can be systematic differences in monitored exposure between site/periods, much the same as a 'study effect'
- Collecting all handler-days from a single site/period 'cluster' could under estimate the scenario diversity.
- Multiple site/periods used

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AHETF Only

Monitoring Data is Already Available for a Number of Scenarios

Purchased Studies: *Not designed specifically for this program, but meet established minimum data quality criteria*

Previous Task Force Studies: *Methodology similar to currently proposed approach*

Some Scenarios are Quite Well Populated Already

New data must be incorporated with existing data in the generic database

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Volunteers Only

The use of (fully and partially) synthetic handler-days makes these non-observational 'intentional dosing' studies.

Requires volunteers only (preferably self-selected)

Anything that can be viewed as 'coercion to participate' (e.g., incentives) are prohibited

With respect to all existing workers, participation/volunteer 'rates' are expected to be extremely small

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Proposed Approach for Obtaining MEs

- Fine tuning of approach used for most studies of this type

  For AHETF: also analogous to that used for previous task force studies

- Purposive Diversity 'Sampling' (PDS) of handler-day conditions (not just workers)

  Handling conditions (including AaiH and workers) are purposively selected and/or scripted

  Purposive selection goal is to maximize diversity, especially in conditions known to influence exposure

  The goal is not to obtain a future exposure handler-day population in miniature

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Purposive Selection of Conditions is Focused on 3 Factors that are Known to Influence Observed Exposures

1. 'Clusters'

AHETF Visits to Different Geographic Locations/Dates

Extent usually <100 miles, <1 week

Provides only opportunity to capture agronomic and other factors that vary over broad geographic extent and dates

AEATF Use of Multiple Site/Periods

Provides an opportunity to capture differences in structure and other factors that vary over multiple buildings and dates

Most important: Clusters capture 'study effects'

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PDS: 3 Factors that are Known to Influence Observed Exposures (continued)

2. Levels of AaiH

   AaiH obviously affects exposure, and impacts normalized exposure indirectly through associated handling conditions

3. Workers

   Worker-worker differences can be very large

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Diversity is Induced for each Scenario

1. M Unique Geographic Location/Period Visits

AHETF

- N monitored handler-days (monitoring units or MUs) obtained from each visit
- These clusters (i.e. visits) are purposively selected to provide diversity in geography, dates, & agronomic conditions

1. M Unique Site/Periods

AEATF

- N monitored handler-days (monitoring units or MUs) obtained at each site/period
- These clusters (i.e. sites) are purposively selected to provide diversity in location, dates, & other relevant conditions

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Diversity (continued)

2. Levels of AaiH

- AaiH strata are established based on the practical range of AaiH in the scenario
- Within each cluster, MUs are distributed evenly across the different strata

AHETF *5 logarithmically-spaced AaiH strata in most AHETF scenarios, 1 MU / stratum*

AEATF *3 task-duration strata in the AEATF mop/wipe scenario, 2 MUs / stratum*

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Diversity (continued)

3. Workers
   - Every MU/ME is a different worker
   - Volunteers are not assigned to scripted conditions for which they have no experience (otherwise a random selection from the volunteer pool is used)

Within each cluster, there is also an informal attempt to reduce homogeneity in other conditions (e.g. equipment used, timing, etc.)

The purpose of this lower level diversification is merely to reduce any within-cluster correlation and is not viewed as critical to the design

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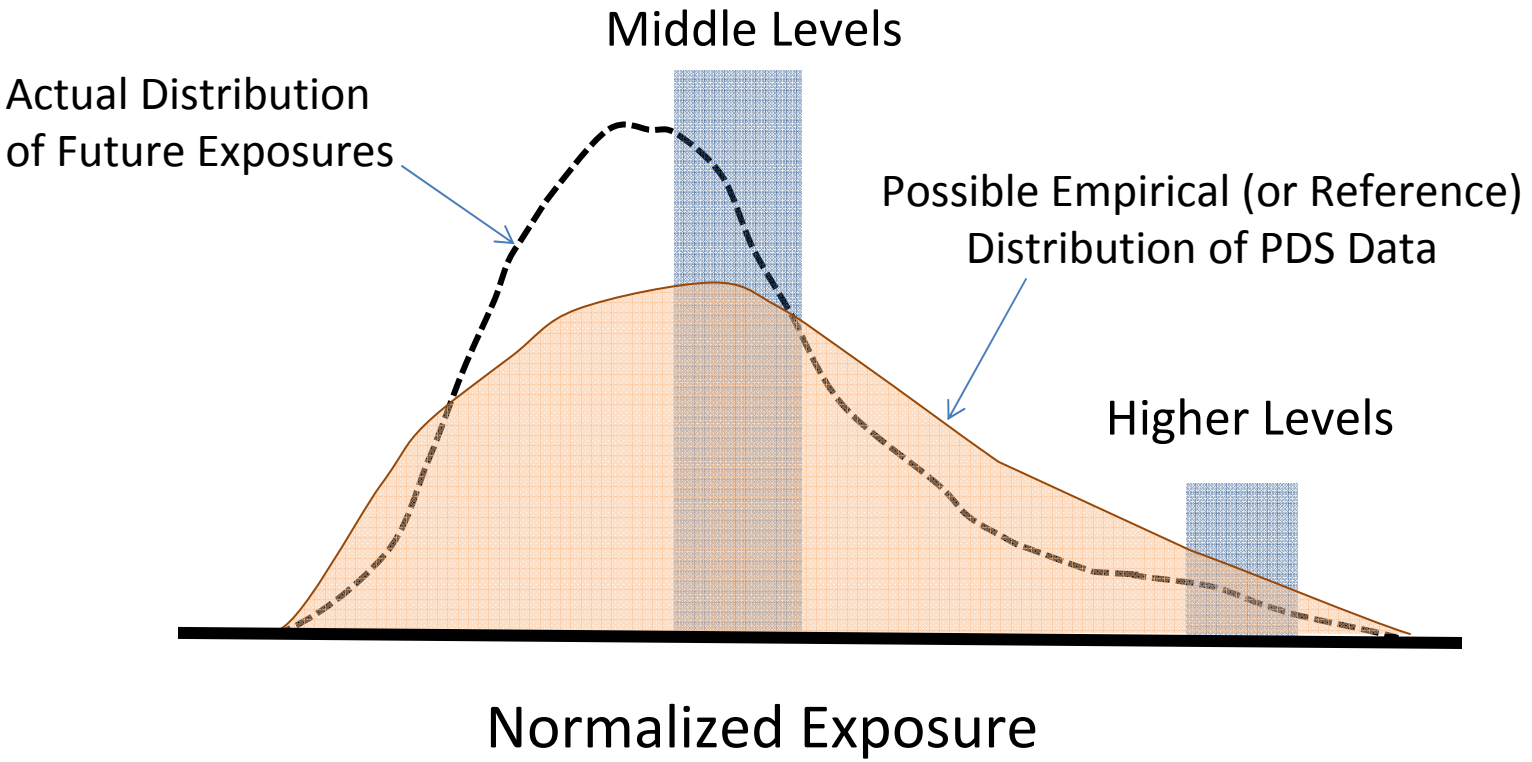
While not a random sample of future handler-days, such 'diversity oriented' data are expected to span the range of potential exposures

… And capture aspects of the future exposure distribution that are of primary value for regulatory purposes



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Sample Sizes

- Set of MUs are not a random sample from an existing population of handler-days
  - *Synthetic monitoring conditions*
  - *Purposive selection from among (self-selected) volunteers*
- Still need some basis for 'calibrating' the effect of a particular sample size
  - *Reference Distribution – a pseudo-random sampling model that is analogous (in some respects) to the purposive sampling process*
  - *A sample size having 'good properties' with this reference pseudo-sampling model is desirable. (Results felt to be reasonable for PDS also)*

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Reference Pseudo-Sampling Model for Normalized Exposures

$$\textit{Log Normalized Exposure} = \textit{Log GM} + A_i + B_{ij}$$

Normal Between-Cluster Effect

Normal Within-Cluster Effect

Normalized Exposures are Lognormal:

GM = geometric mean

GSD = total geometric standard deviation

ICC = intra-cluster correlation

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AHETF

Reference Sampling Model & Sample Sizes

Benchmark Accuracy Goal:

Sampling estimates of mean and 95th percentile of the reference distribution would be within 3-fold of true values (with 95% probability)

From existing data: *GSD ≈ 4* *ICC ≈ 0.3*

Results from Numerous Simulation Studies:

M=5 clusters, with N=5 MUs per cluster

Also OK if M·N=25 as long as N ≤ 5

Total N and #/cluster → Budget Exceeded

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AEATF Reference Sampling Model & Sample Sizes

Same 3-fold Accuracy Benchmark Goal

From limited existing data and other assumptions for the mop/wipe scenario:

GSD = 2.86 *ICC ≤ 0.3*

Indications from Simulation Studies:

M=3 clusters, with N=6 MUs per cluster

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AHETF Only

Secondary Benefit of Proposed Design

- With reference sampling model, M=5, N=5, a 10x range in AaiH, and the proposed AaiH stratification:

  A regression analysis would provide at least 80% power for distinguishing AaiH proportionality from independence (i.e., no relationship)

- This allows some assessment of the (marginal) relationship between exposure and AaiH

  Nice to know, but not viewed as a primary data adequacy objective

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Why Purposive and Not Probability Sampling?

- In principle, random sampling could yield data-based estimates of error for mean and percentiles

  Random sampling ≠ Randomization

- Avoid claims of 'manipulation' of results to reduce exposure (Random allocation is used whenever feasible)

- It might be claimed that the data are in some sense 'more representative' of some population

  Representative in the probability sense

  Not in the commonly-assumed 'mini-me' sense

  Or in the 'surrogate/generic' sense

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Why Not a Probability Sample?

A probability sample from what?

Target population is not existing handler days, but predicted future handler-days

Surrogate Chemicals: *Exposure is only directly measured for surrogate chemicals, and these are only a small portion of all the chemicals used*

Synthetic Conditions: *Although workers are members of an existing handler population, the handling conditions may be synthetic*

AHETF *e.g. chemical a applied at lower-than-typical rate to simulate conditions more common for chemical b*

AEATF *e.g. chemical used at single concentration but task duration varied to simulate conditions existing throughout scenario*

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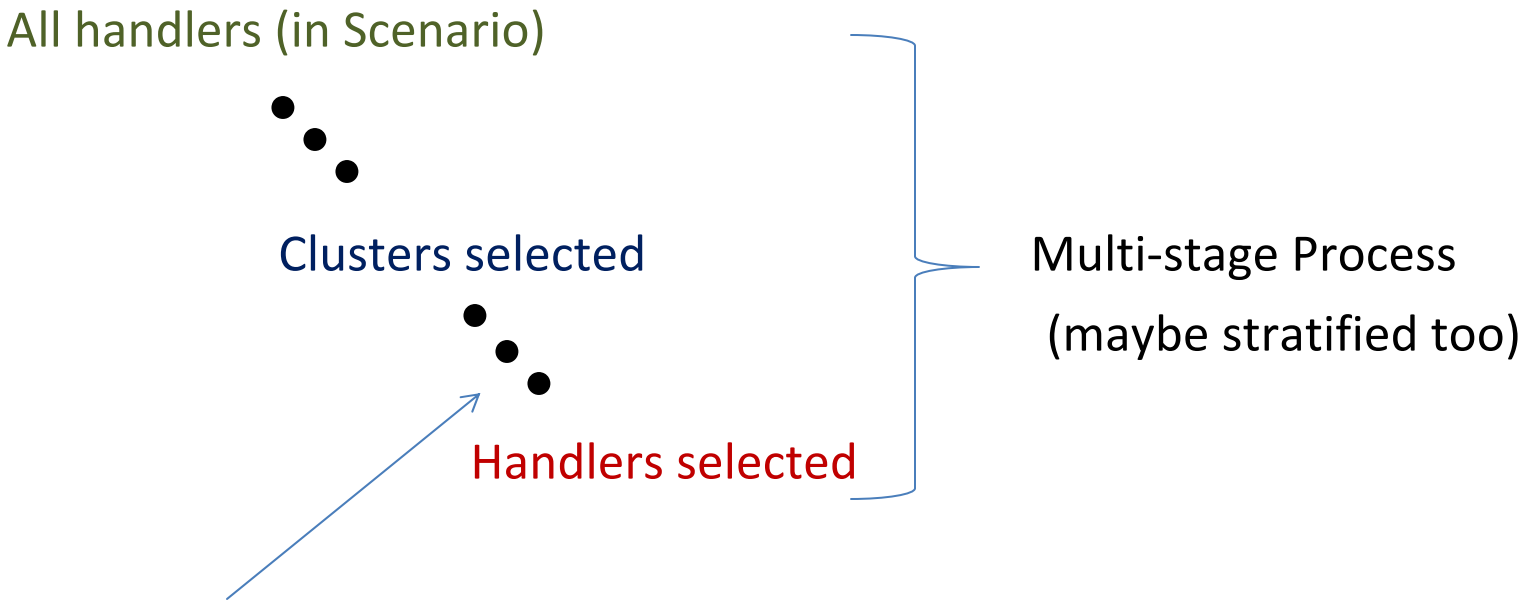
Probability Sample of Only Handlers?

It is certainly possible, in principle, to obtain probability sample of <u>workers</u> from an existing population of all handlers



Involves listing ALL possible handlers that could perform the scenario tasks (although this listing could be performed in stages)

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Probability Sample of Handlers?

- The within-cluster listing operations and resulting overhead just to identify a handful of potential subjects would result in unacceptable increases in cost and time

  e.g. Qualified agricultural handlers are often extremely rare and quite difficult to locate and recruit

- Selecting a probability sample of subjects and 'convincing' them to participate is not the same as 'volunteering'

  Some ethical limitations on usual random sampling methods

  Self-selection is incompatible with random selection

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Probability Sample of Handlers?

- A probability sample of just subjects might not be of much value when other handling conditions are not part of the sampling process.

  Especially when much of the existing AHETF data is PDS

  Partially random sampling ≠ random sampling

- Would likely not be a simple random sample of subjects

  Unlikely to have a sufficient sample size and structure to estimate standard errors without making simplifying assumptions

- Given the expected low volunteer rate, synthetic conditions, etc., is there really much practical advantage to 5-6 randomly chosen workers in a cluster compared with 5-6 that are purposively chosen?

  Small random samples are unlikely to capture diversity

  Small participation rates destroy 'representativeness'

  Listing overhead → greater costs

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Summary

- The proposed methodology is expected to adequately cover the range of future exposures under a scenario
- The cost of the currently proposed (PDS) program is at the limits of affordability for both task forces.
- Additional costs can only come at the expense of reducing the number of scenarios monitored. (This would force many members to withdraw from the task forces.)
- There is no obvious advantage to adding a 'partial' probability sampling component to a set of synthetic future handler-days…especially if it increases the cost of the program and/or delays activities