Understanding temporal variation in exposures to chemicals

Paul Price
National Exposure Research Laboratory
U.S. EPA, Office of Research and Development

Temporal Exposure Issues for Environmental Pollutants: Health Effects and Methodologies for Estimating Risk
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Purpose: To present key concepts that will be expanded in later talks

1. Understanding the relationship between exposure, dose, and internal dose
2. Inter- and intra-individual variation in exposure
3. Temporal variation across lifestages and across short-term periods
4. Sources of variation in exposure and dose
5. Characterizing temporal variation of internal dose
6. Implications of exposure variation for the risk assessment process

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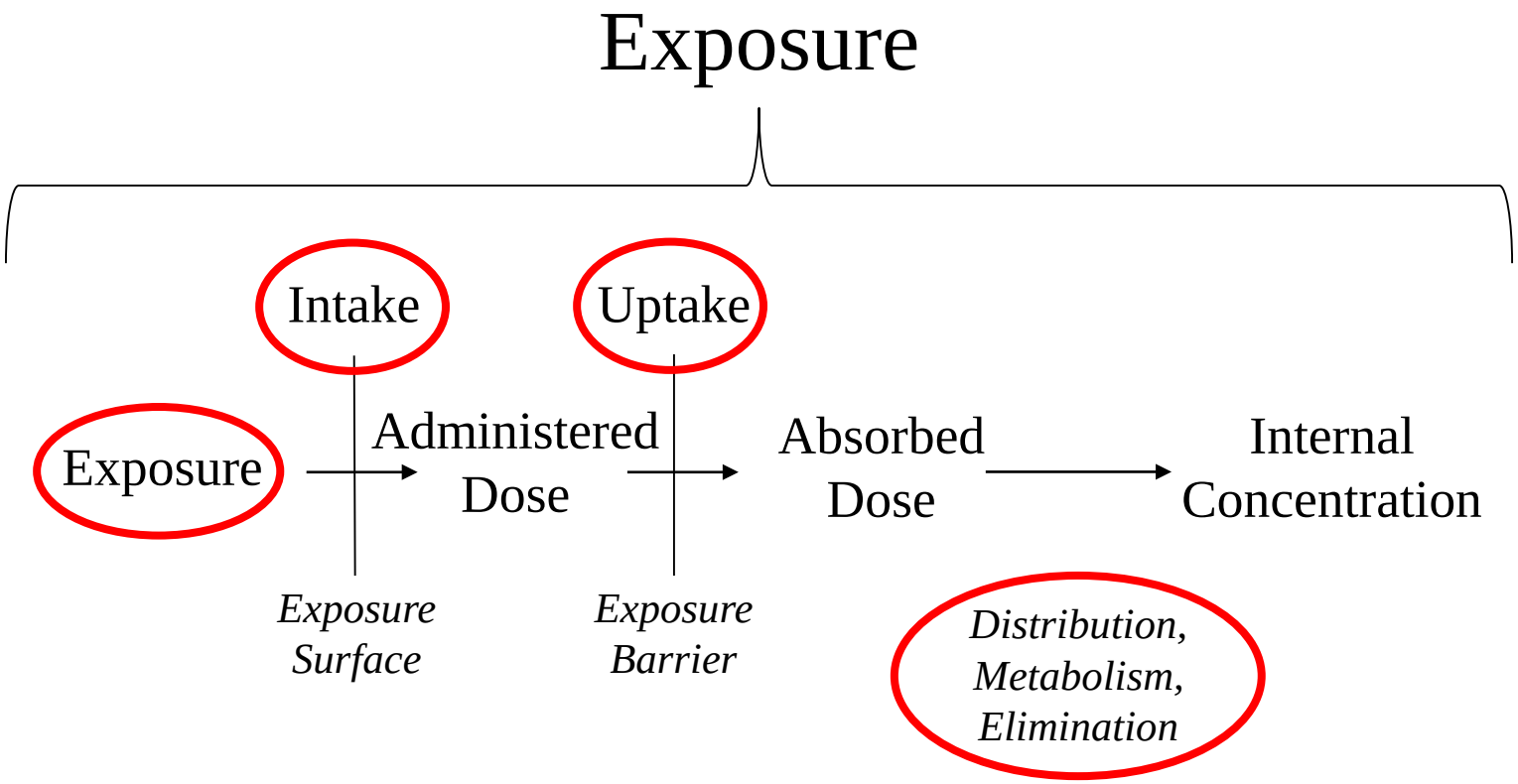
Understanding exposure

- The risk assessment process defines risk as a function of both “hazard” and “exposure”
  - No hazard – no risk
  - No exposure – no risk
- Exposure, however, is a complex process
- Nomenclature we use to describe exposure is confusing
  - Exposure is used as a general term (exposure vs. hazard)
  - Exposure also defined as “a concentration of a chemical at the exposure surface over some duration of time” and is one of several metrics use in the exposure process

Understanding exposure



Exposure Surface

- *Skin, mouth, nose*

Exposure Barrier

- *Skin, GI track, lung*

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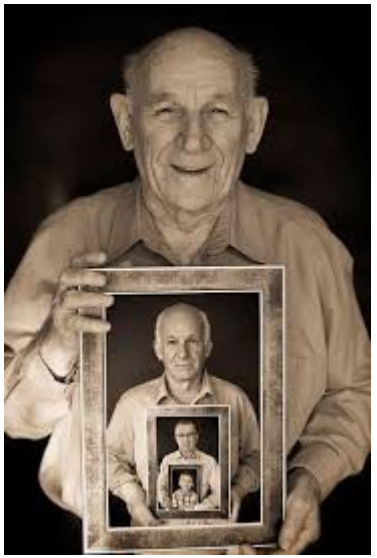
Near-field and far-field exposures

- Near field sources
  - Use of consumer products,
  - Chemicals in diet,
  - Indoor sources (heating, cooking, etc.)
- Far field sources
  - Sources that that release chemicals to air, water, or biota and that require environmental transport
- Near field sources have been shown to cause larger doses than far field sources and tend to drive total exposures for certain chemicals

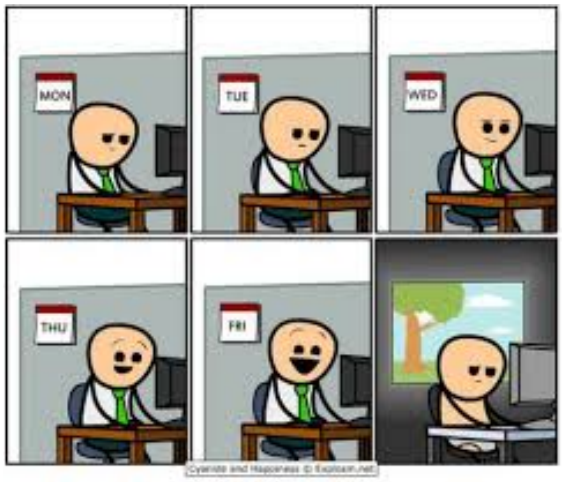
Inter-individual variation in exposure and dose

- Variation in acute and chronic exposures *across* individuals
  - Interindividual variation due to differences in location, behavior, physiology, and metabolism
  - A key strategy to is to focus assessment on (sub)populations of concern
- Populations of concern can be defined by exposure potential or toxicological sensitivity

Intra-individual temporal patterns in exposure and dose



- Examines how exposures and dose change over time for a single individual.
- Two time scales for variation:
  - Periods in an individual's life (lifestages)
  - Short term variation (hour-to-hour or day-to-day)
- Variation across lifestages is important for
  - Identification of sensitive populations
  - Determination of life-time average daily doses
- Variation in an individuals that occur over short periods of time (day-to-day)
  - Used to determine acute and annual average daily doses for individuals in a specific lifestage



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Temporal variation across lifestages

- The exposure potential of various lifestages varies by source
  - Infants
    - Fluid intake in newborns on a body weight basis is 3-5 times higher then adults
  - 1-3 year olds
    - Highest intake of food related exposures on a body weight basis (pesticides and food additives)
    - Highest rate of oral exposures to contaminants in soil, dust, or on surfaces
    - Breathing zone exposures are closer to the ground
  - Adults use more types of products containing a wider range of chemicals
  - Adults over 30 years of age
    - Long term exposures to local sources (longest time spent in one residence)
- Metabolism varies with age
  - Ontogeny of enzyme systems
- In general, separate exposure assessments should be performed for each relevant life stages

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Short-term temporal variation

- There are multiple components to the exposure assessment process
  - The presence of the chemical at the exposure boundary;
  - The rate of intake;
  - Adsorption; and
  - Distribution, metabolism, and excretion
- All of these components can vary over short periods of time for an individual
- Short term temporal variation in dose will be driven by the combined effects of the components

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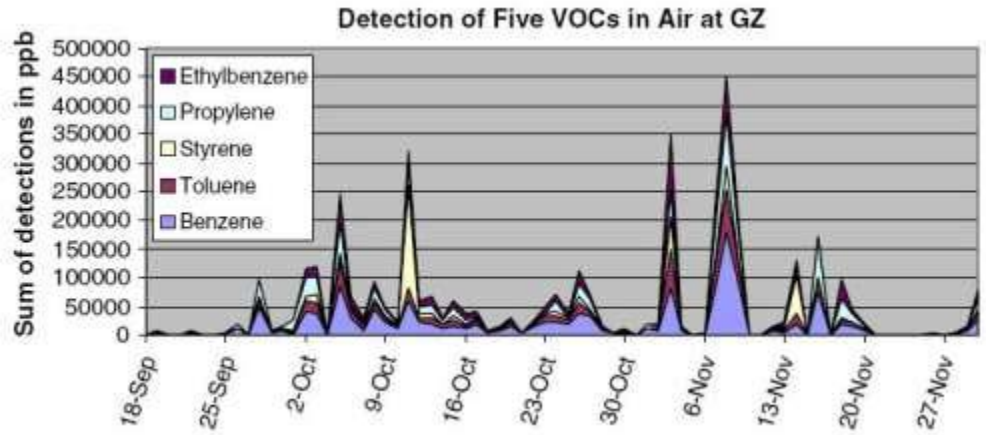
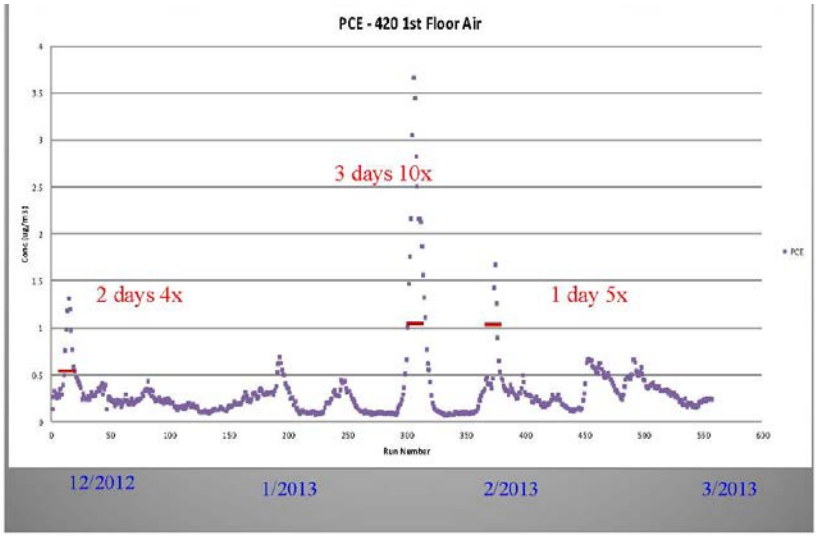
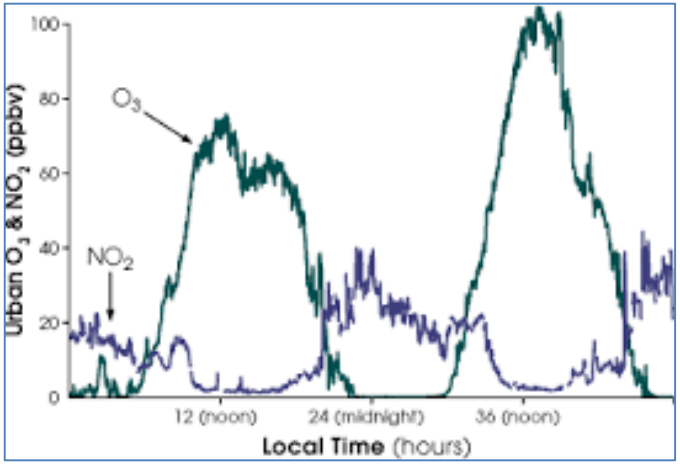
Outdoor and indoor air levels vary over time



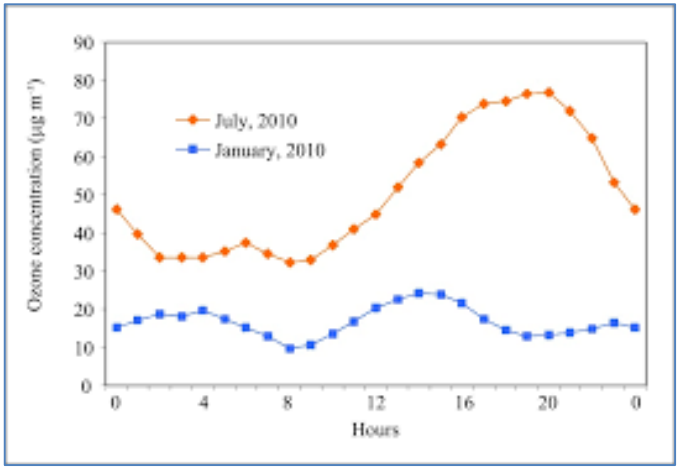


Variations can be cyclic

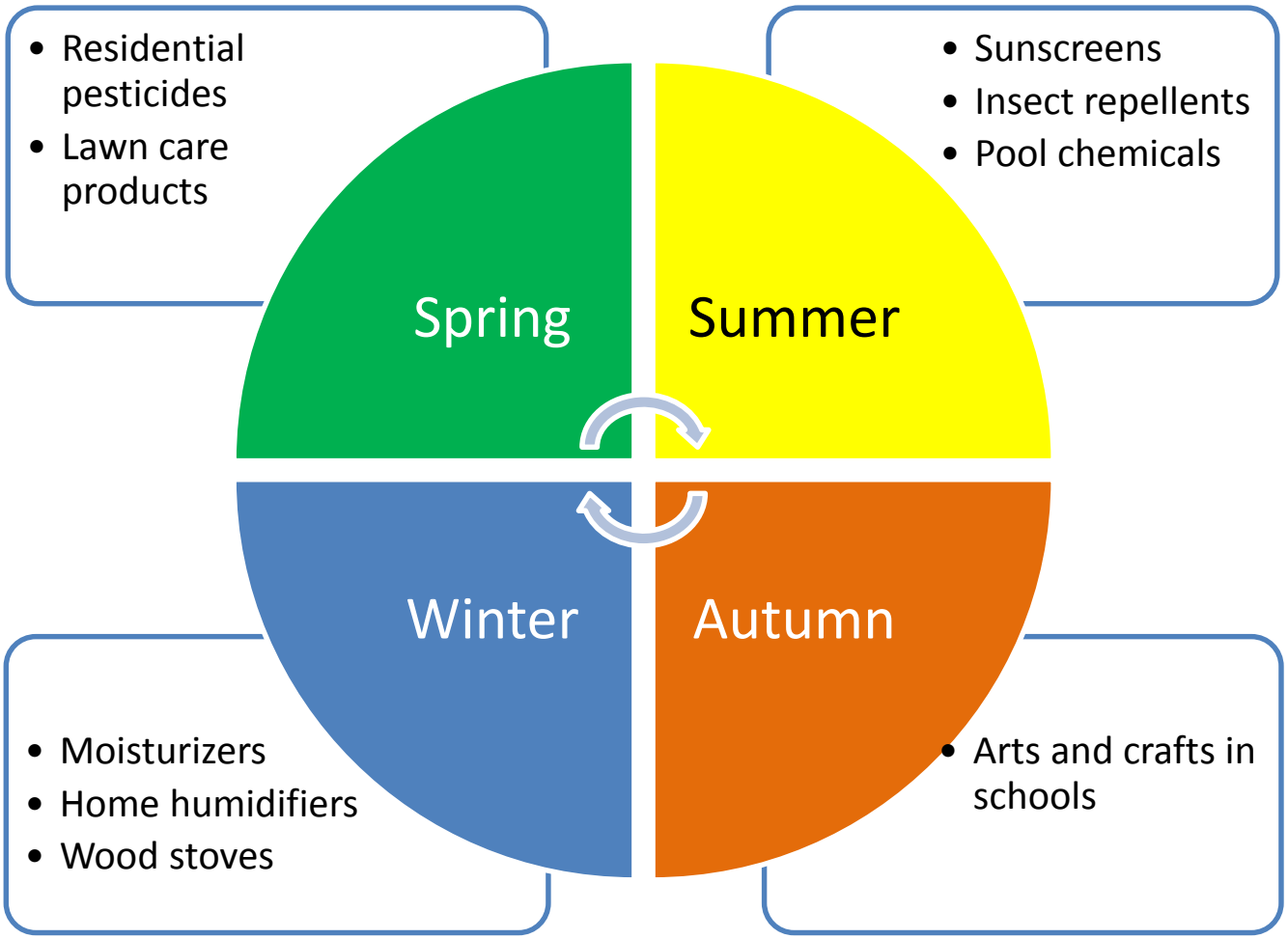
- Diurnal variation in air pollutants



- Seasonal variation in mean and diurnal variation



Seasonal use of consumer products



Seven day cyclical patterns of exposure related behaviors

- Week days
  - Work-related exposures
  - Transportation-related exposures
- Use of multiple product use tends to cluster on non-work days (week-end warriors)
  - Paint, spackling, and paint remover
  - Yard products
  - House cleaning products

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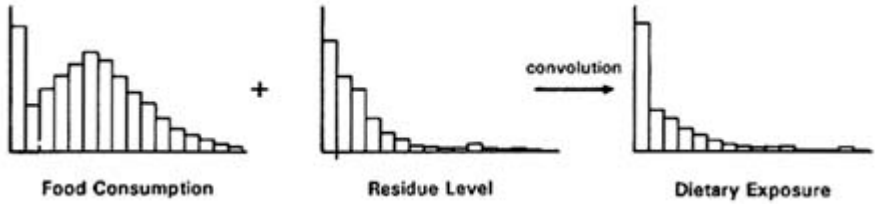
Short-term variation in ADME

- Processes that determine absorption, distribution, and elimination are thought to be relatively stable over short periods of time (day-to-day)
  - Function of individual's physiology, and
  - Physical and chemical properties of the substance
- Metabolism, however, can vary over time
  - Circadian cycles of enzyme activity
  - Activation or deactivation enzyme systems can occur as a result of agents in diet (alcohol, grapefruit juice, etc.)

Temporal variation in dietary doses of pesticides

- To receive a large dose of a pesticide requires:
  - Consumption of large amounts of a food item
  - Large residue level in the food item



- Individuals diets change from day-to-day and residues vary from item-to-item
- The result is that longitudinal doses of pesticides for an individual tend to be skewed
  - Most doses are modest in size compared to a few high exposure events, or
  - Many days of zero exposure and a few days of non-zero exposure.

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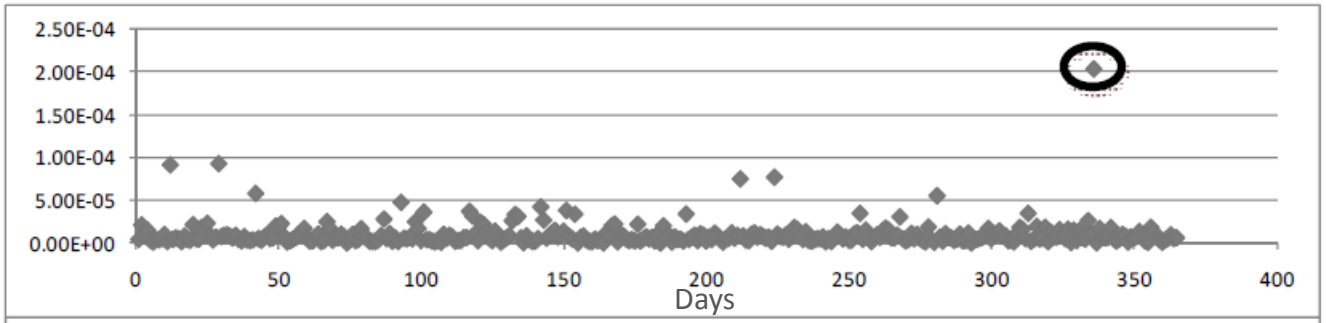
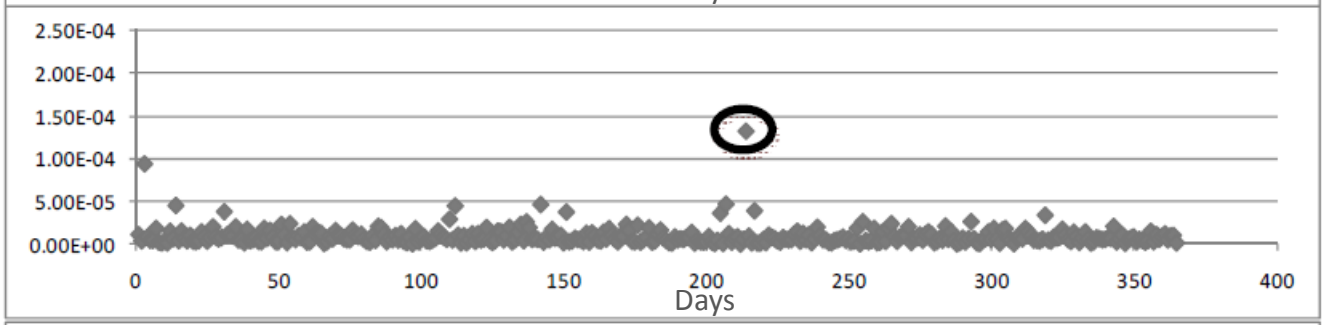
Prediction of daily dietary doses of a pesticide over a year

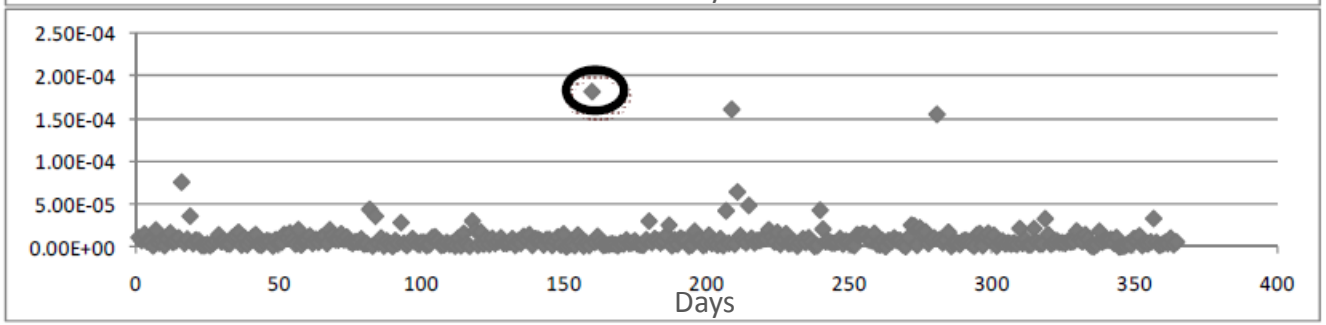
Person A



Person B



Person C

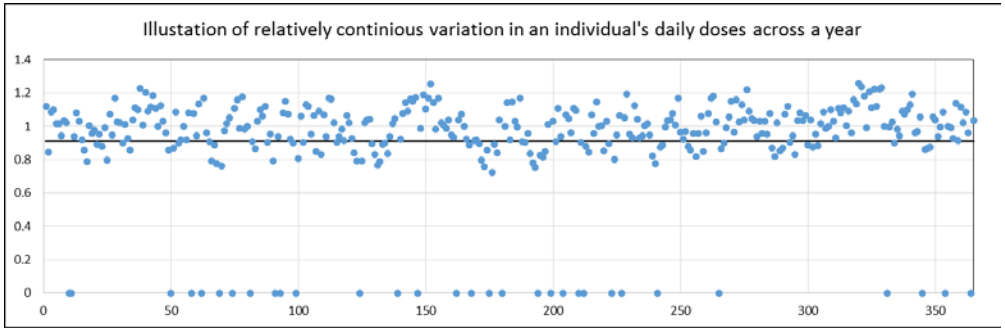


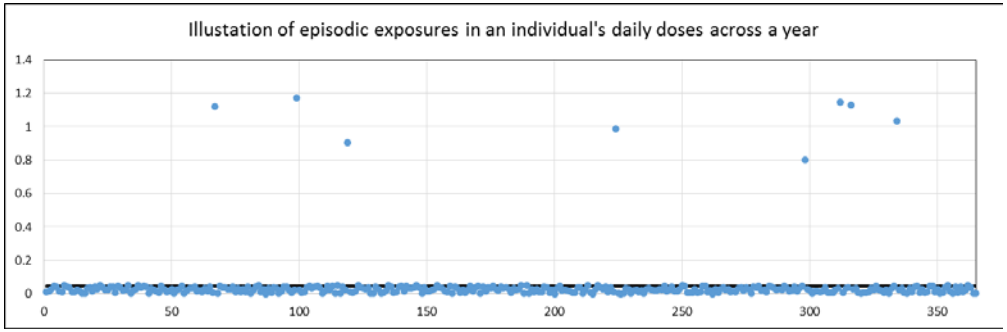
Juberg et al. 2011

Temporal patterns of administered dose

There are two extremes in temporal variation of dose:

- Constant dose:
  - Exposure contaminants in drinking water derived from ground water
  - Exposure to chemicals in frequently used consumer products (toothpaste)
  - Lipophilic compounds in breast milk
- Episodic doses
  - Infrequently used consumer products
    - Fireplace cleaning products
  - Exposures with highly variable source concentrations and intake rates
    - Recreational use of rivers
    - Pesticides residues in diet





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Episodic exposures and risk

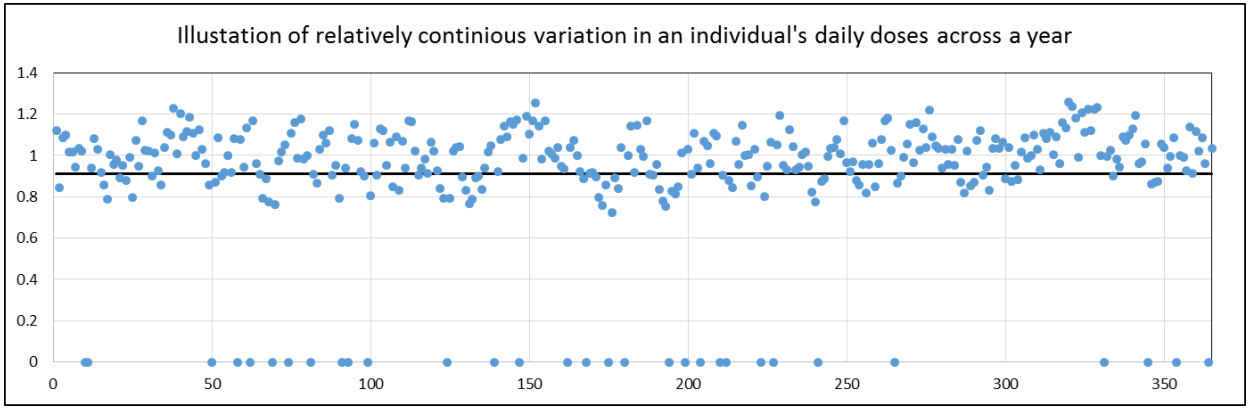
- When exposures are episodic the risk assessor needs to determine if the effects from one dose will dissipate before the next dose
- This decision will be informed by:
  - Kinetic information (will the body burden return to background or *de minimis* level prior to the next exposure?)
  - Data on the reversibility of early key event in adverse outcome pathways (will the biology of the individual return to a background state)

Characterizing temporal exposure

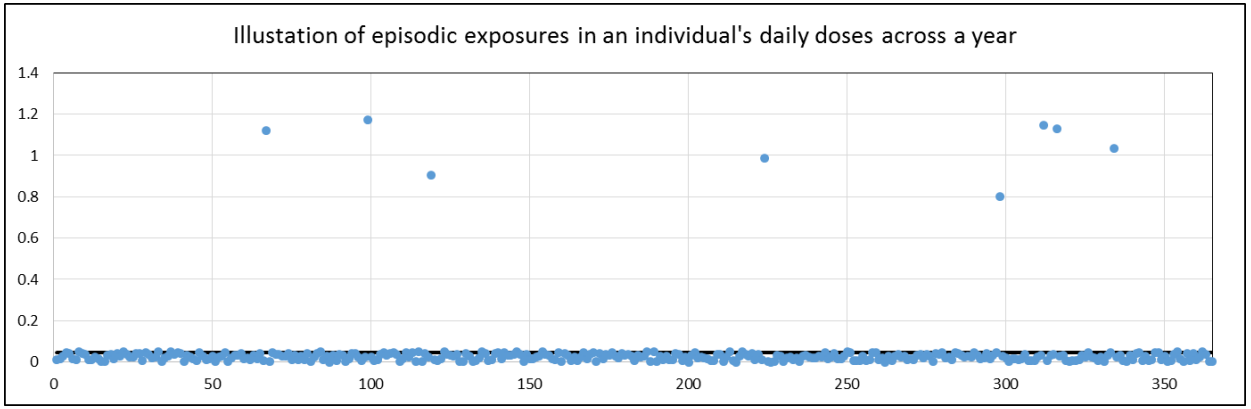
- A useful approach is to estimate the Peak To Average PTA ratio of dose rates

PTA = Peak daily dose/ Average dose

Longitudinal variation and the risk assessment process



Peak / average = 1.5



Peak / average = 20

Characterizing temporal exposure

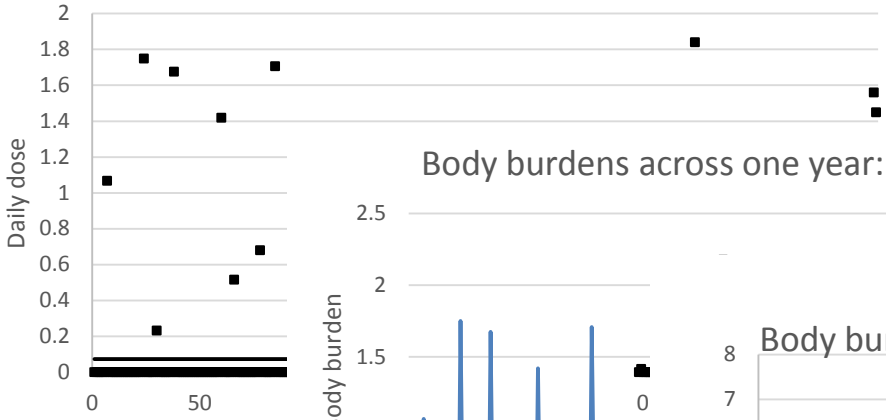
- A useful approach is to estimate the Peak To Average PTA ratio of dose rates

  PTA = Peak daily dose/Average dose

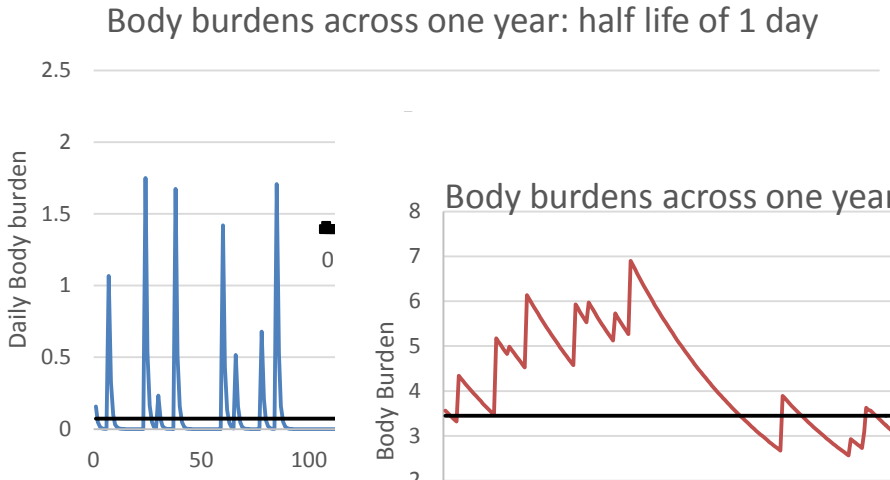
- When the ratio of peak to average dose is greater than the ratio of the acute to chronic permitted dose
  - Management of chemicals is driven by acute toxicity
- As a result:
  - Dietary pesticides are typically regulated based on acute effects
  - Drinking water exposures are regulated based on chronic effects

Temporal patterns of internal and intake doses

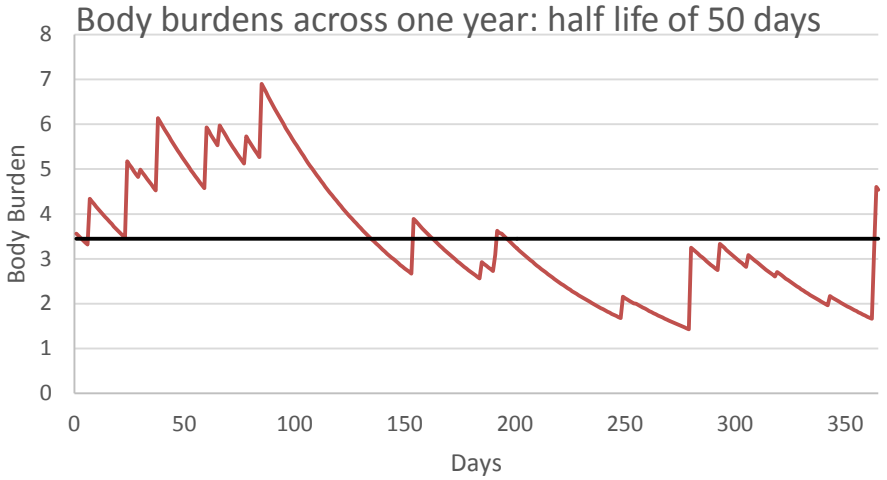
The impact of temporal variation decreases for chemicals with long half-lives in the body



Ratio = 37



Ratio = 27



Ratio = 2

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Summary

- Exposures, doses, and internal doses vary over time
  - Sources of exposure and human behaviors both vary over time
  - Variation can be episodic or cyclical
- Variation occurs across lifestages and across days or hours
- The degree of short term variation differs with source and exposed population
  - Some are relatively continuous
  - Some are highly episodic
- For direct acting chemicals, long half lives lessen the impact of temporal variation
- Episodic exposures pose a challenge to risk assessors
  - Requiring data kinetics of the compound and the dynamics of early events in the AOPs

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Questions?