The Science Behind the PFAS Drinking Water Health Advisory and How It Affects Risk Management Decision Making

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USEPA DRINKING WATER HEALTH ADVISORIES

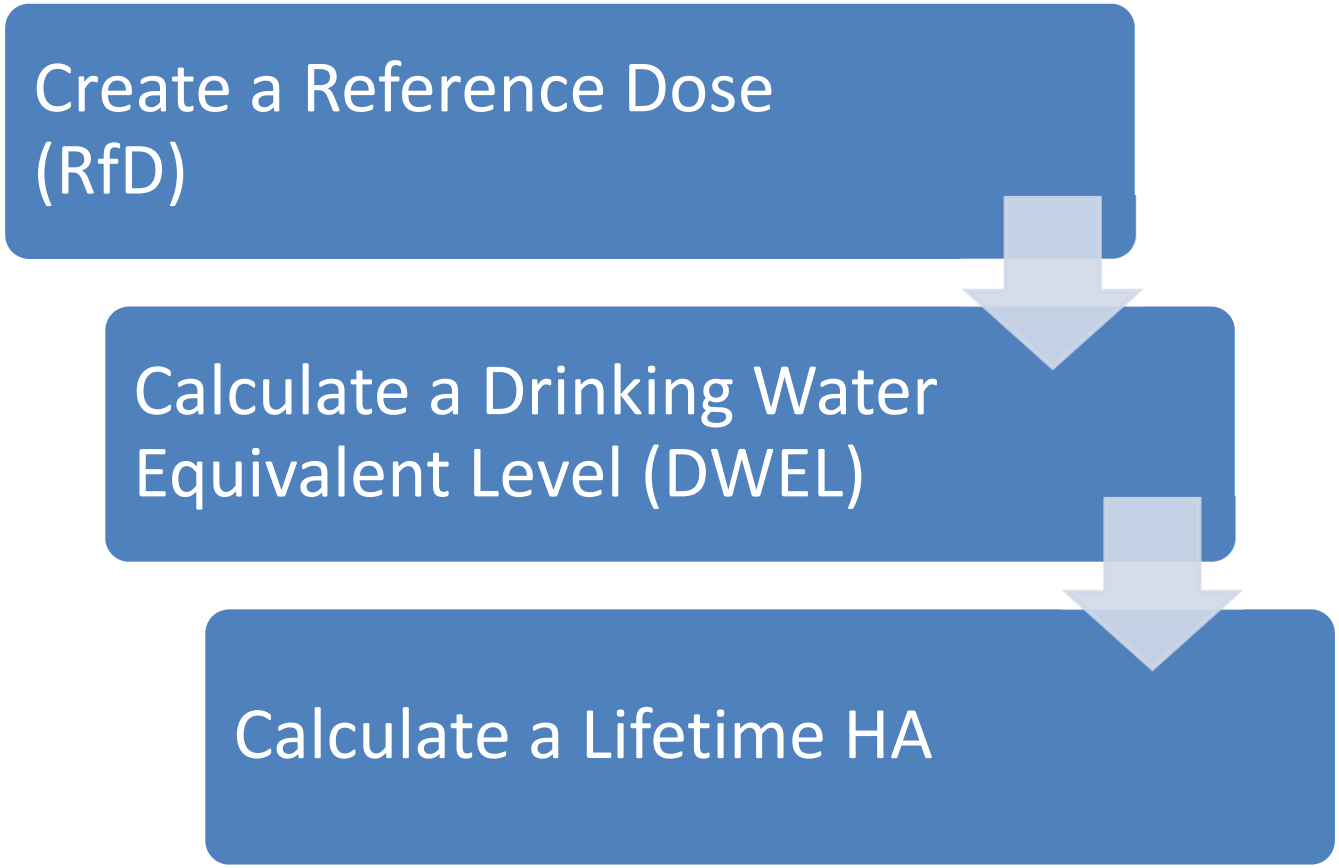
- 2009 Provisional Health Advisory
  - 0.2 µg/L for PFOS
  - 0.4 µg/L for PFOA
- May 2016 Health Advisory
  - 0.07 µg/L PFOA
  - 0.07 µg/L PFOS

What was the basis for the revised values and what are some of the uncertainties in their development?

How do these uncertainties affect the decision making process?

APPROACH FOR CALCULATING HEALTH ADVISORIES

- Three Step Process
- Same process used for PFOA and PFOS



CREATE A REFERENCE DOSE

- Reviewed toxicological research
  - Peer-reviewed studies
  - Animal and human epidemiological
- Developed a toxicity reference dose (RfD)
  - Estimate of the daily exposure to humans that is likely to be without adverse effects during a lifetime
  - Threshold dose

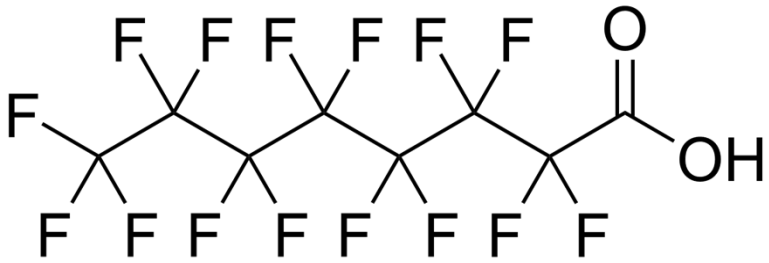
$$RfD = \frac{HED_{NOAEL} or HED_{LOAEL}}{UF}$$

Where:

- HED = Human equivalent dose from the modeled serum concentration representing either a NOAEL or LOAEL experimental dose (mg/kg/day)
- UF = Total uncertainty factor (unitless)

TOXICITY BACKGROUND FOR PFOA RFD

- RfD derived from developmental toxicity study in mice, critical effects include:
  - Reduced bone tissue formation in extremities
  - Accelerated puberty in male pups following exposure during gestation and lactation
- Other toxic effects identified in animal studies include:
  - Developmental effects
  - Liver toxicity
  - Kidney toxicity
  - Immune effects
- Human epidemiological data report the following associations:
  - High cholesterol
  - Increased liver enzymes
  - Decreased vaccination response
  - Thyroid disorders
  - Pregnancy-induced hypertension and preeclampsia
  - Testicular and kidney cancer



TOXICITY BACKGROUND FOR PFOS RFD

- RfD derived from developmental toxicity study in rats, critical effect was decreased body weight in pups following exposure during gestation and lactation
- Other toxic effects identified in animal studies include:
  - Developmental effects
  - Reproductive effects
  - Liver toxicity
  - Developmental neurotoxicity
  - Immune effects
  - Thyroid and liver cancer

- Human epidemiological data report the following associations:
  - High cholesterol
  - Thyroid disease
  - Immune suppression
  - Reduced fertility
  - Some studies suggest an association with bladder, colon, and prostate cancer – literature is inconsistent and some studies are confounded failure to control for other risk factors

CALCULATE DWEL

- The DWEL assumes 100% of exposure comes from drinking water
- Ingestion scenario
- Residential

$$DWEL = \frac{RfD \times bw}{DWI}$$

Where:

- RfD = Reference dose (mg/kg/day)
- bw = body weight (kg)
- DWI = Assumed human daily drinking water intake (L/day)

CALCULATION OF LIFETIME HA

- Factors other sources of exposure
- Relative source contribution
  - 20% Drinking water
  - 80% Other sources

$$Lifetime\ HA = DWEL \times RSC$$

- Where:
  - DWEL = Drinking water equivalent level from Step 2 (mg/L)
  - RSC = Relative source contribution (unitless)

PROCESS SEEMS SIMPLE, BUT…

- Tox Studies with target endpoints
- Simple Math:
  - $RfD = \frac{HED_{NOAEL} or HED_{LOAEL}}{UF}$
  - $DWEL = \frac{RfD \times bw}{DWI}$
  - $Lifetime\ HA = DWEL \times RSC$

…PFAS ARE NOT SIMPLE

- PFAS have complex pharmacokinetics (PKs) that make data interpretation difficult
  - Absorb easily through the digestive tract
  - Distribute throughout the body by bonding with plasma proteins
  - No clear evidence of metabolism
  - Rate of excretion varies by species and gender
- Half-life varies widely by species and gender
- Very long half-life in humans due to reabsorption in kidneys
  - ~2-3 years for PFOS
  - ~4-8 years for PFOA
  - Rate of excretion can vary by isomer with branched chains have less resorption than linear

WHY DO COMPLEX PKs MATTER?

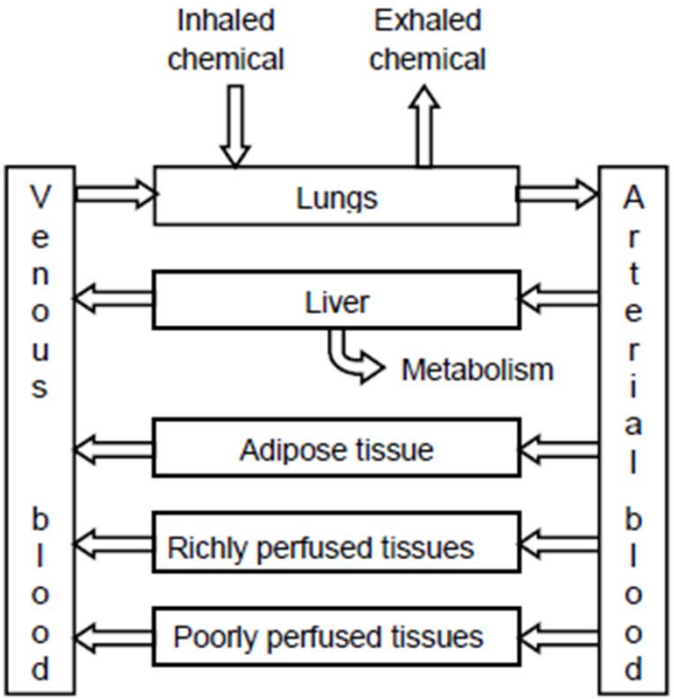
- Differences in PKs across genders or species produce differences in the external dose needed to achieve the same internal dose

In other words…

- If the same chemical stays in a human for longer than it stays in a rat, the human is going to end up accumulating more chemical in his/her blood than the rat will over time (assuming constant doses, etc.)
- If the same amount of chemical in the blood will cause the same toxic effect in the human and the rat, and the human and the rat are exposed to the same amount

HOW IS VARIABILITY ADDRESSED IN HAs?

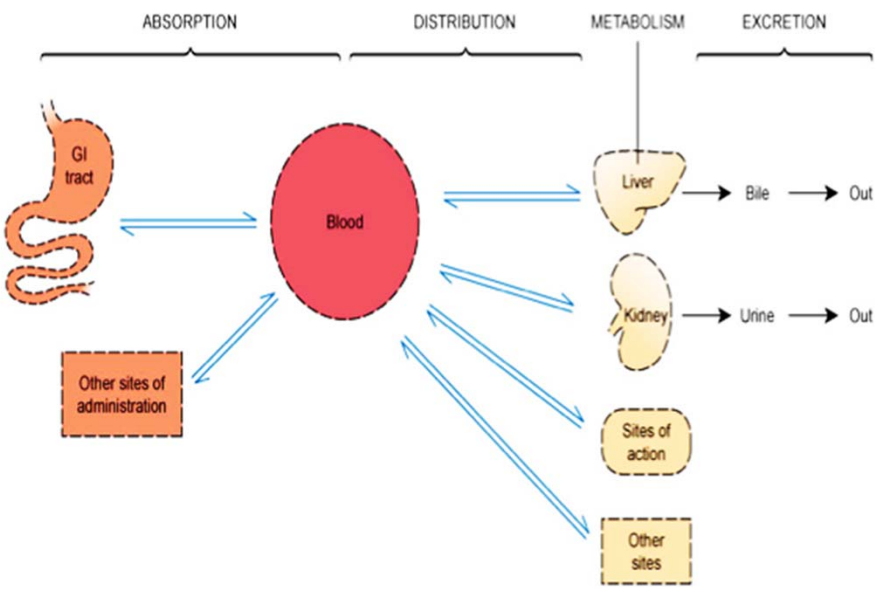
- RfDs were developed using physiologically-based pharmacokinetic (PBPK) modeling
- Models are commonly used and considered scientifically defensible



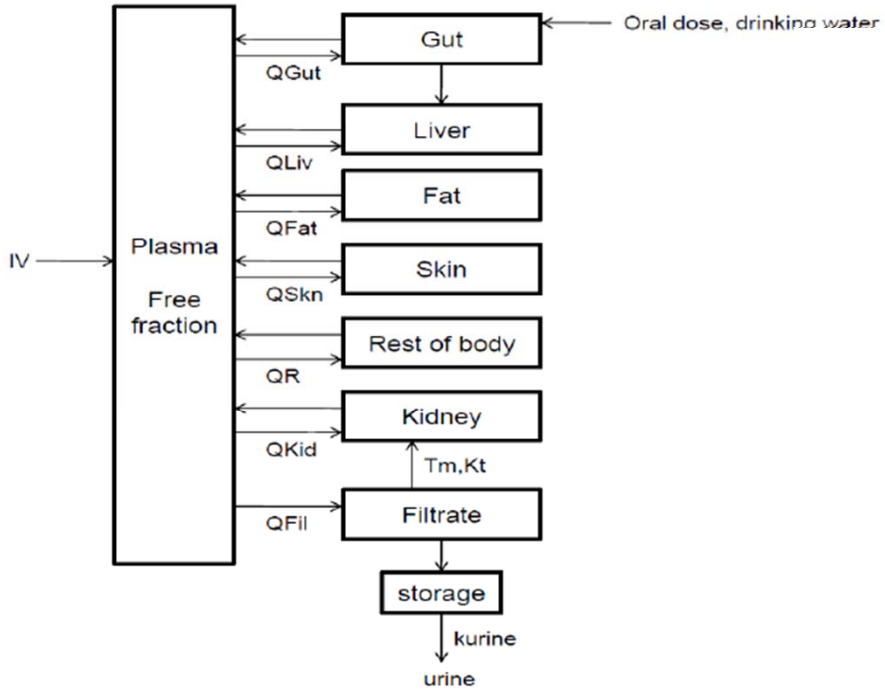
From: EPA/R-05/043F, August 2006

WHAT ARE PBPK MODELS?

- Simulate the absorption distribution, metabolism, and excretion of chemicals that enter the body
- Estimate internal doses
- Multiple uses in risk assessment
  - Interspecies extrapolation
  - Route-to-route extrapolation
  - Estimation of toxicity from unevaluated conditions
  - Dose extrapolation



EXAMPLE OF PBPK MODELS FOR PFOA



Notes:
T_m = transporter maximum, K_t = affinity constant, and Q = flow in and out of tissues.

Figure 2-7. Structure of the PFOA PBPK Model in Monkeys and Humans

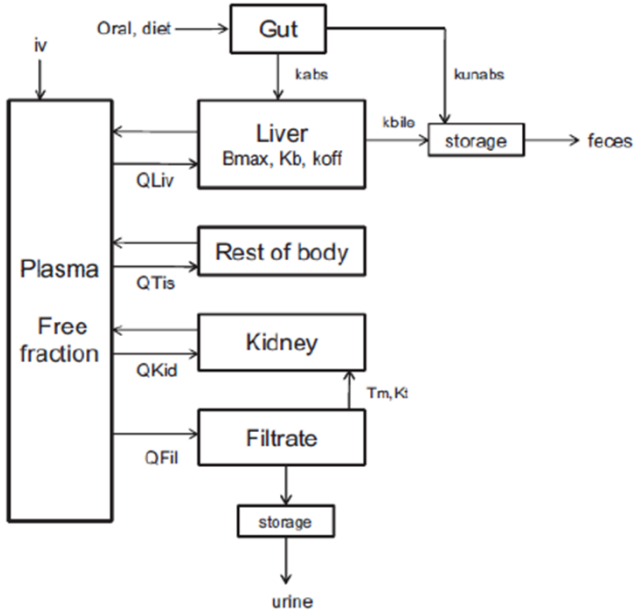


Figure 2-8. Structure of the PBPK Model for PFOA in the Adult Sprague-Dawley Rat

From: EPA 822-R-16-003, May 2016

AREAS OF UNCERTAINTY

- Toxicological research uncertainties
- Calculation methodology
- Limitations in PBPK Modeling
- Incorporating ongoing research

TOXICOLOGICAL RESEARCH UNCERTAINTIES

- Limitation in database
- Cross-species interpretation
- Dose extrapolation
- Population size
- Genetic diversity
- Multiple chemical interactions
- Etc.

- Standard areas of uncertainty that we deal with on a routine basis

LIMITATIONS IN PBPK MODELING

- Uses simplifying assumptions to translate experimental situations to modeled calculations
  - Steady-state blood concentrations
  - Continuous dosing concentrations
- Assumes toxic effects in animals are directly relevant to humans
  - Epidemiological data
  - Mechanistic data
- Multiple chemical interactions

CALCULATION METHODOLOGY

- Remember the basis of the HAs!

- HAs are LIFETIME values
- Assumptions differ from standard risk assessment methodology
  - Based on lactating women
  - No time factor

- Health Advisory document provides methodology for calculation short duration/acute exposure HAs

WHAT ABOUT…


research
development
analysis
technology
information
experiment
laboratory
science
discovery
data
chart
work
search
symbol
thinking
biology
discover
medicine
computer magnify
scientific
study
inspiration
market
education
chemistry
hypothesis
expertise
test
chemical
business
solution
ideas
analytics
web
lens
equipment
biological
strategy
trial
analyzing
creativity
examine
marketing
plan
customers
researching
icon
concept
magnifying
industry
sharing
person
design
analyze
words
enlarge
survey
knowledge
researcher
scientist
sample lab
innovation
growth
medical
investigation
teamwork

HOW DO WE ADDRESS THESE UNCERTAINTIES?

- Add layers of conservatism?
  - Combine “worst case” assumptions from multiple models?
  - Assume equal sensitivity across species?
  - Practicality?
  - Implementability?
- Avoid “one size fits all” approaches
  - Apply site-specific risk assessments
  - Consider appropriate land and water uses
- Avoid stagnation of cleanup levels
  - Revisit toxicological database regularly
  - Non-drinking water scenario cleanup levels?
  - Revisit source contribution assumptions?
- Avoid stagnation of cleanup decisions

GET IN TOUCH WITH US

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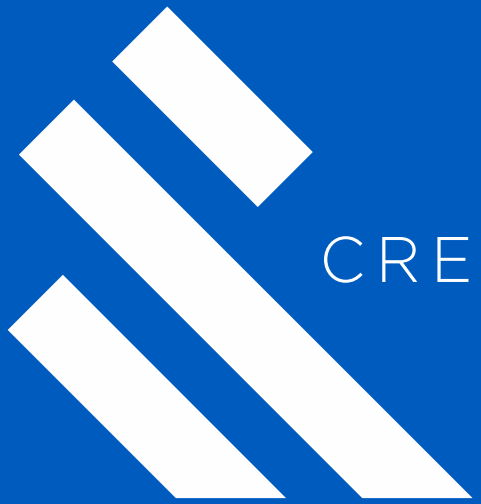

CREATE AMAZING.