Overview of an Integrated Modeling System for Supporting Multiscale Source-to-Effect Studies of Human Health Risks

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Outline

• Overview of Integrated Modeling in the Source-to-Effect Continuum
  • MENTOR – Modeling ENvironment for TOtal Risk studies
  • DORIAN – DOse Response INformaion ANalysis system

• Overview of MENTOR
  • MENTOR-1A (“One Atmosphere”)
  • MENTOR-3P (Physiologically based Population Pharmacokinetics)
  • MENTOR-2E (Emergency Events)
    - Case study showing model uncertainty and “fast” modeling
  • MENTOR-4M (Multimedia, Multipathway, Multiroute, and Multichemical)
    - Integrated modeling case study using MENTOR-4M coupled with 3MRA

• Brief Overview of DORIAN
A mechanistically consistent infrastructure for both exposure assessment and health impact analysis: CERM/MENTOR and ebCTC/DORIAN address the source-to-outcome continuum.

This schematic has evolved from various graphical representations of the source-to-outcome sequence, that were developed in recent years by USEPA.

**CERM:** Center for Exposure and Risk Modeling
**MENTOR:** Modeling ENvironment for TOtal Risk studies
**ebCTC:** environmental bioinformatics and Computational Toxicology Center
**DORIAN:** DOse-Response Information Analysis system
A major issue in implementing consistent source-to-dose modeling is sequentially going to “local/neighborhood/personal resolution”

Source: 3MRA User Guide 2002

Source: Georgopoulos et al., ES&T, 1997, 31(1)
Analysis of exposures to environmental contaminants, and of subsequent doses and effects is typically a multiscale problem in terms of both the environmental/microenvironmental and the biological processes involved.

**Example: Air Pollution**

- **Continent, State, County**
- **Community**
- **Neighborhood**
- **Indoor/Individual**
- **Organ**
- **Cell/Molecule**
- **Tissue**
Spatiotemporal patterns of surface formaldehyde (top) and benzene (bottom) concentrations predicted by CMAQ (at 12 km resolution) for January and July of 2001.
MENTOR-1A estimates of the 90th percentile of seasonal averages of daily personal formaldehyde (top) and benzene (bottom) intake (“dose”) (μg) due to outdoor air for Winter and Summer of 2001.
The physiologically based toxicokinetic modules of MENTOR-3P aim to characterize cumulative & aggregate exposure, uptake and target tissue dose for multiple chemicals and for physiology with intra- and interindividually variation and variability. Modules of different levels of complexity for specific organs/tissues and alternative formulations for different types of contaminants are available in the MENTOR system.
Example demonstrations of MENTOR-3P:
(a) simultaneous exposure to multiple metals
(b) exposure of pregnant female and fetus to MeHg

Standard 70 kg male consuming a 1 mg oral dose each of As(V), Cr(VI), MeHg, Pb, and Cd.

Standard 65 kg female consuming 65 μg methylmercury per day (gestation at day 1250)

Simulated concentration profile of chemicals and metabolites in the liver of a standard reference male ingesting a mixture of metals.

Simulated concentration profile of methylmercury for a pregnant woman and fetus. The physiological parameters of both the maternal and fetal systems are changing over time.
Summary of Source-to-Dose-to-Effect Analysis of Emergency Events Involving Inhalation Exposure to Chemical & Biological (Non-Contagious) Agents Using MENTOR
Estimated Individual Biological Doses of Anthrax
Comparison of MENTOR/SHEDS Results With Standard/Traditional Techniques

Delaware, Jan 19, 2001

Estimates based on 100g release over 1 hour (left) and over 10 hours (right)
Probability of Anthrax Infection for Individuals
Comparison of MENTOR/SHEDS Results with Simplifying Approximations

Estimates based on 100g release over 1 hour (left) and over 10 hours (right)

Estimates of total potential infections:
• 1 hour release:
  MENTOR/SHEDS: 926; EPA EFH assumptions: 5,353; Craft et al. assumptions: 10,893
• 10 hour release:
  MENTOR/SHEDS: 876; EPA EFH assumptions: 6,427; Craft et al. assumptions: 13,804
Expected Number of Anthrax Infections
For a 100g Release Over Period of 1 Hour, Averaged Per Census Tract

Release starting at 08:00 hours, January 19, 2001, calculated with (a) MENTOR/SHEDS, (b) inhalation rates from Exposure Factor Handbook (USEPA, 1997), and (c) inhalation rates from Craft et al., 2003
MENTOR/SHEDS: 926; EPA EFH assumptions: 5,353; Craft et al. assumptions: 10,893
Expected Number of Anthrax Infections
For a 100g Release Over Period of 10 Hours, Averaged Per Census Tract

Release starting at 08:00 hours, January 19, 2001, calculated with (a) MENTOR/SHEDS, (b) inhalation rates from Exposure Factor Handbook (USEPA, 1997), and (c) inhalation rates from Craft et al., 2003
MENTOR/SHEDS: 876; EPA EFH assumptions: 6,427; Craft et al. assumptions: 13,804
Fast, Equivalent Modeling through Pre-Computed Modeling
Motivation: Performing multiple model runs with a major subset of options staying constant
Steps in “pre-computed” module application

S1: Regular model execution flow
S2: “Full model run” for pre-computing tables
S3: Subsequent, “fast” model runs
The MENTOR framework for assessing cumulative/aggregate exposures and doses for multiple multimedia contaminants

1. Estimate multimedia background levels of environmental pollutants (air, water and soil) through either:
   a. multivariate spatiotemporal analysis of monitor data
   b. multiscale environmental modeling

2. Estimate local multimedia pollutant levels in an administrative unit (such as a census tract) or a conveniently defined grid through either:
   a. field study measurements
   b. subgrid “adjustments” of regional model estimates
   c. application of a local scale environmental model

3. Characterize attributes of populations (geographic density, age, gender, race, income, etc.)
   a. select fixed-size sample population that statistically reproduces essential demographics
   b. or divide population of interest into exhaustive set of cohorts

4. Develop activity event (or exposure event) sequences for each member of the sample population or of each cohort for the exposure period through either:
   a. existing databases from composites of past studies (for baseline assessment)
   b. study-specific information (special registries)

5. Estimate multimedia levels and temporal profiles of pollutants in various microenvironments (residences, offices, restaurants, streets, vehicles, etc.) through either:
   a. field study measurements
   b. microenvironmental mass-balance modeling (air), drinking water distribution modeling (water), dietary exposure modeling (food)

6. Calculate appropriate inhalation rates, as well as drinking water and food consumption rates for the members of the sample population, combining the physiological attributes of the study subjects and the activities pursued during the individual exposure events

7. Biologically based target tissue dose modeling (toxicokinetics and toxicodynamics)

US Census, US Housing Survey, Local Data
CHAD, NHAPS
ICRP and Other Physiological & METS Databases, CSFII, NHANES
Conceptual framework of the evolving 3MRA system:
Using 3MRA as a screening system in MENTOR/SHEDS-4M applications

Collaboration with G. Laniak (USEPA) and K. Castelton (Battelle)
Case Study: Consideration of hypothetical As and TCE releases from a Hazardous Waste Site in Franklin County, OH
HWS Demonstration Case Study: 3MRA-derived estimates of site contributions to TCE groundwater concentration levels
HWS Demonstration Case Study: 3MRA-derived estimates of site contributions to Arsenic groundwater concentration levels
HWS Demonstration Case Study: 3MRA-derived estimates of site contributions to TCE ambient air concentration levels
HWS Demonstration Case Study:
MENTOR/ SHEDS-derived estimates of site contributions to the
distribution of As doses for the population in the vicinity of the site

(a) Cumulative arsenic (inorganic) exposure distributions from background (including inhalation, food intake, drinking water ingestion, and non-dietary intake) and a hazardous waste site (drinking water route) for the near-site population of Franklin County, Ohio

(b) Cumulative arsenic tissue dose distributions of kidney and liver for the near-site population of Franklin County, Ohio
HWS Demonstration Case Study:
MENTOR/SHEDS-derived estimates of site contributions to the
distribution of TCE doses for the population in the vicinity of the site

(a) Cumulative TCE exposure distributions from background and the additional contribution of a hazardous waste site for the near-site population of Franklin County, Ohio
(b) Cumulative TCE tissue dose distributions of liver for the near-site population of Franklin County, Ohio
Revisiting: A mechanistically consistent infrastructure for both exposure assessment and health impact analysis: CERM/MENTOR and ebCTC/DORIAN address the source-to-outcome continuum.

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DORIAN: DOse-Response Information Analysis system
Consortium Members:
UMDNJ, Rutgers, Princeton, and USFDA
Some Concluding Remarks

• Consistency in the context of Integrated Modeling as a driving force
  • A main principle of MENTOR and DORIAN
• Modularity and use of open standards
  • Use of the most appropriate module for a given modeling step
  • Alternative, screening level formulations
• Characterization of uncertainties
  • Using traditional or computationally efficient alternatives
  • Multiple types of uncertainty of different origins
• Providing fast equivalent modeling systems for faster applications
  • Formal lumping methods
  • Reduced modeling using “pre-computed” models
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