FQPA mandated that all exposures to consumers be aggregated for determination of safety (the unreasonable certainty of no harm).
EPA calculates a DWLOC on the basis of how much room is left over in the risk cup after considering dietary exposure:

\[ \text{DWLOC (µg/L)} = \frac{\text{Chronic water exp. (mg/kg/d)} \times \text{Body wt. (kg)}}{10^3 \times \text{mg/µg}} \]

**Methyl Parathion Drinking Water Assessment**

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Water Monitoring Data (µg/L)</th>
<th>cPAD (mg/kg/d)</th>
<th>Chronic Food Exposure</th>
<th>Chronic Water Exposure (mg/kg/d)</th>
<th>DWLOC (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Male</td>
<td>0.009</td>
<td>0.000020</td>
<td>0.000002</td>
<td>0.000018</td>
<td>0.63</td>
</tr>
<tr>
<td>Adult Female</td>
<td>0.009</td>
<td>0.000020</td>
<td>0.000005</td>
<td>0.000015</td>
<td>0.45</td>
</tr>
<tr>
<td>Infants &lt;1 yr</td>
<td>0.009</td>
<td>0.000020</td>
<td>0.000006</td>
<td>0.000014</td>
<td>0.14</td>
</tr>
<tr>
<td>Children 1-6</td>
<td>0.009</td>
<td>0.000020</td>
<td>0.000009</td>
<td>0.000011</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Acute Exposure**

**Residential Exposure Assessment—Applying**

\[ \text{PDR} = \text{UE} \times \text{AR} \times \text{A} \]

- **PDR** = potential dose rate (mg/day)
- **UE** = unit exposure (mg/lb Al)
- **AR** = application rate (lb Al/acre; lb Al/gallon)
- **A** = area treated (acres/day or gallons/day)

**Exposure** = PDR/kg body weight
- (mg/kg/day)

**Toxicity Endpoints**
- Acute
- Short-Term

**Exposure (mg/kg)**

- **Food Exposure**
- **Drinking Water Exposure**
- **Residential Exposure**
- **Total Aggregate Exposure**

**Time (Days)**
**Residential Exposure Assessment--Post Applying**

- Dislodgeable residue (from surface or foliage) – µg or mg per unit area (cm²)
- Dermal Transfer Coefficient (Tc)
  - Designates how much surface area is exposed in a unit time
  - cm²/hr
- Length of contact (hr)
- Fraction of residue dissipating daily (rate)

**Biomonitoring for Chlorpyrifos Exposure**

![Chemical structure of Trichloropyridinol (TCP)]

- Volunteers carry out “residential activity”
  - Extract clothes
  - Extract gloves; wash hands
  - Air monitoring in breathing zone using portable sampler
  - Assess biomarkers
    - For ex., metabolite in urine
      - Back calculate whole body exposure

**Estimated Residential Exposure (mg/kg/day)**

- **Dursban**
  - **Spray**
  - **Granular**

**Cumulative Exposure & Risk Assessment**

- FQPA mandates cumulation of exposure from pesticide residues having a common mechanism of toxicity
  - Pertains to two or more pesticides or other substances that cause a common toxic effect(s) to human health by the same, or essentially the same, sequence of major biochemical events
  - Do not confuse with a common toxic effect
    - Same toxic effect in or at the same anatomical or physiological site or locus, but not necessarily by the same biochemical mechanism

**Rationale**

- “A person exposed to a single pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause the same toxic effect by a mechanism as that of the subject pesticide, even if the exposure levels to the other substances are also considered safe.”
- Assumes dose additivity is the only interaction
  - No synergism, antagonism, nor neutrality
Cumulative Toxicity

- Cumulative toxicity represents the net change in toxicity that results from the combined exposure to multiple chemical substances relative to the toxicity caused by each substance alone.
- Factors influencing:
  - Exposure pattern—temporal co-occurrence of same MOA residues
  - Toxicokinetics
  - Duration of common toxic effect
  - Interactions between the substances causing the effect

EPA revised the CRA and released a new report during June 2002

http://www.epa.gov/pesticides

The Process

- Analyze exposure scenarios
  - Food
    - USDA Pesticide Data Program database
    - Assume nationally uniform consumption (CFSII database)
    - Contains subpopulations to be assessed
      - 1-2 years, 3-5 years, 20-49 years, >50 years
  - Drinking water
    - 7 EPA regions (based on geographic specificity of commodities grown; climatic similarities)
    - Modeling output data using PRZM and EXAMS
  - Residential (non-occupational)
    - 7 EPA regions
    - Proprietary data, PHED, or published studies
    - National use statistics

Seven EPA-Defined Regions of U.S. Used for Conducting Drinking Water Exposure Assessment

Numbers by EPA Region
Letters represent the USDA 12 Farming Regions

Percent of Samples with Indicated Number of Residues

<table>
<thead>
<tr>
<th>Residues</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-96</td>
<td></td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percent of Samples with Indicated Number of Residues

<table>
<thead>
<tr>
<th>Residues</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple Juice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>1994-98</td>
<td></td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Drinking Water & Non-Occupational Exposure

- Less well studied than food residues
- Temporal variation
- Geographic variation
  - For water exposure, choose a “representative” vulnerable watershed basin in each of the seven EPA regions based on previous detections, use of OPs, runoff potential
- Must be modeled on a one-day time step, similarly to food residue exposure
  - Use of Calendex, a proprietary model that integrates all exposure scenarios across time

Combining Residues

- Choose Point of Departure (PoD)
  - The point on the dose-response curve that signifies an effect definitively tied to a dose
    - Below the PoD, the responses are usually modeled mathematically, not directly observed
- ED10 (Effective Dose to 10% response) or the BMD10 (Benchmark Dose for 10% response)
  - Dose giving 10% inhibition of brain acetylcholinesterase (female, 21 day or greater)
  - Determined by fitting response data to exponential function

Basic Exponential Dose-Response Model for Estimating 10% ChE Inhibition Benchmark Dose (BMD10)

\[
y = A \left( P_0 + \left( 1 - P_0 \right) e^{- n \text{ Dose}} \right)
\]

Combining Residues

- Normalize individual OPs to same potency using index chemical
  - Methamidophos (Monitor) chosen as index chemical
- Calculate RPF (relative potency factor)
  - \[ \text{RPF} = \frac{\text{BMD10} \text{ index}}{\text{BMD10} \text{ chemical}} \]
  - Relevant for oral dose-response exposures only
  - For dermal and inhalation, use the Comparable Effect Level (CEL)
    - Corresponds to 15% inhibition response relative to control animals in dermal and inhalational exposure studies
    - Analogous calculation for the RPF

Dealing with the FQPA 10X Factor

- For most of the OPs, EPA decided to incorporate an extra 3X FQPA safety factor by increasing the size of the RPF by 3
  - Result is to make potential exposure three times bigger

Female BMD10s (Dose Inhibiting Brain AChe by 10%)
Male/Female BMD10s

Relative Potency Factors Based on Female Brain Acetylcholinesterase Inhibition

Exposure Determination

- Multiply RPF by residue concentrations resulting from each exposure scenario to create index equivalent residue
- Sum all the index equivalent residues for each exposure scenario
- Add all index equivalent residues across exposure scenarios employing a one-day time step for each individual modeled by Calendex
- Repeat modeling for each person represented in the CFSII database

Cumulative Risk Characterization

- The MOE approach is used wherein exposure is compared to the NOAEL for the index chemical, methamidophos
- As opposed to a single chemical RA, EPA does not conclude that exposure exceeded their levels of concern (i.e., the risk management benchmark)
- EPA plots the daily MOE relative to the percentile of exposure

Note: overall MOE @ 99.9th percentile of exposure lies somewhere between 100 & ~50
**EPA’s Conclusions**

- Drinking water contributed very little to cumulative exposure.
- Residential exposure was the major contributor to cumulative exposure:
  - DDVP pest strips (inhalation exposure)
  - Hand-to-mouth behavior in children
- Certain foods contributed more to dietary exposure than others (for example, grapes, apples, pears).
- Even with the extra FQPA safety factor of 3 incorporated into the RPFs, MOE for 1-2 year old was about 50 or greater.