Lecture 11  Pesticides: Human Health Risk Assessment

I. Characterizing Risk Depends on Estimating Exposure to Pesticide Residues
   A. Unless exposure has been high enough to cause acute poisoning and definite signs & symptomology, detection of human health effects is difficult.
      1. Attempts to characterize potential chronic effects like cancer or reproductive outcomes has relied on epidemiological studies.
         a. Unfortunately, the vast majority of chemical epidemiological studies for chronic effects relies on surrogate or “remembered” exposure data, not empirical exposure data.
      2. Many studies have attempted to extrapolate rodent toxicological studies to human health effects.
         a. Recall that rodents (and more infrequently dogs) are used in the hazard identification step of risk assessment.
         b. But the doses given to rodents are very high relative to environmental exposures, and it is also prolonged at nearly constant high levels.
            1. The studies are excellent for determining the comparatively most sensitive endpoint (under the circumstances of the experimental exposure) and for understanding mechanistically toxicodynamics.
            2. But, do typical hazard identification studies reflect risk (i.e., probability of an adverse effect) to humans (in all age groups)?
   B. Thus, to estimate hazard (and characterize risk) to humans, exposure data is needed.
      1. The exposure can be modeled, it can be directly measured, or it can be estimated using a combination of empirical data and probabilistic modeling.
   C. Under the FQPA (Food Quality Protection Act) of 1996, Congress mandated EPA to reassess all tolerances for registered pesticides and determine if they were safe to consumers.
      1. Within these mandates, Congress specifically told EPA that it would examine in aggregate all dietary exposure, drinking water exposure, and residential exposure (if an active ingredient was registered for residential indoor or outdoor use).
      2. Congress also mandated that EPA would cumulate residue exposure if two or more different active ingredients had the same mechanism of toxicity.
         a. For example, organophosphorus (OP) and carbamate insecticides both inhibit acetylcholinesterase but the kinetics of enzyme recovery are very different (OPs slow, carbamates fast).
         b. EPA had to develop a science policy for cumulating exposures to multiple OP insecticide residues on food or in water, but the OPs were of different potency.
   D. EPA’s strategy for estimating exposure to consumers (recall that the FQPA did not specifically include workers nor fish & wildlife) was to consider all sources: food, water, home & garden.
      1. The agency uses a metaphor of the body as a cup or vessel that is filled to various degrees with pesticide residue exposure (known as the “risk cup”).
2. The very brim of the cup is equivalent to the Reference Dose (RfD) or Population Adjusted Dose (PAD). To overflow the cup with exposure is to exceed the RfD or PAD.
   a. For chronic (everyday) exposure, the EPA has estimated that food accounts for 80% of the total; water accounts for 10%; and residential use of pesticides (whether by professional applicator or homeowner) accounts for 10%.
   b. Note that the EPA was required by the FQPA to use an extra safety factor (known as the FQPA safety factor) of up to 10-fold if the hazards of a pesticide were greater for infants/children than adults at a given dose.
      1. In other words, if a toxicological test showed that neonatal or juvenile rats exhibited some toxicological endpoint (for ex., acetylcholinesterase) inhibition at a lower dose than an adult rat, then EPA would be obligated to apply the extra safety factor.
      2. In some cases, EPA would weight the evidence and severity of the response and place less than the 10X extra safety factor (typically 3X).
      3. In many cases, no extra safety factor needed to be applied.
      4. If the extra safety factor was applied to the RfD, then the newly calculated “safe” dose would be called the Population Adjusted Dose (or PAD).
         a. Thus, the total maximum safety factor would be 1000 rather than 100 so that the most sensitive populations are protected (if warranted by the results of the toxicological studies).

![Risk Cup Metaphor](image)

**Figure 1.** The risk cup metaphor. Note that the FQPA mandates EPA to adjust the RfD by an extra safety factor up to 10X if infants/children are assessed as being more sensitive than adults. This extra protection could also apply to reproductive age females.

**II. How Is a Tolerance Developed and Validated? Basic Procedures**

A. First, remember that each food commodity on which a pesticide is proposed for use must have a tolerance for residues.

B. The manufacturer actually petitions the FDA (which collaborates with the EPA) for a food tolerance; in the petition the manufacturer actually proposes the tolerance and the EPA than assesses the validity of that tolerance.

   1. The proposed tolerance is derived from numerous crop residue tests that companies are required to carry out;
   2. The pesticide must be tested in enough regions of the U.S. to represent proportionally the acreage where the commodity is grown;
a. The tests are usually worst-case for producing residues because multiples of the proposed recommended rate will be applied, and harvest of the commodity will occur very close to application (at least at the minimum proposed “pre-harvest interval” or PHI, referring to the time between the last legal pesticide application and harvest of the crop)
   1. For example, if the application rate of a pesticide is 1 kg ai [active ingredient] per acre, than 2, 3, or 4 kg ai/acre might be applied in addition to the 1 kg;
   2. The pesticide may be applied within a few days of crop harvest, even though the manufacturer may eventually desire to have the product used with a different PHI.
   3. The manufacturer examines the residue data and then proposes the tolerance a bit higher; if it wasn’t set higher than the maximum residues found in field testing, then growers would face a risk of exceeding the tolerance, given the variability of sampling and conditions that would affect pesticide residue dissipation.

C. A mathematical game called the Theoretical Maximum Residue Contribution (TMRC) is first used to determine the adequacy of tolerances for new compounds. The TMRC is a Tier I analysis (there are four tiers based on detail of data used; see discussion below); it assumes the worst case of exposure (because all residues are at the tolerance on all commodities for which registration is sought; in reality, however, the tolerance concentration which hardly ever occurs on marketed food).
   1. Two basic pieces of information must be measured or assumed;
      a. **The Reference Dose (RfD)**, defined as the exposure below which there a reasonable certainty of no adverse effects. The units of the RfD are mg pesticide/kilogram body weight/day, or mg/kg/d (this can also be expressed as µg/kg/d). The RfD is actually the benchmark that EPA uses to calculate (characterize) risk.
         1. The RfD is based on the NOAEL derived from various subchronic and/or chronic toxicological studies with rats, mice, or dogs. The NOEL is then divided by an uncertainty factor. This factor is usually 100. Under the FQPA, this factor might be 10 times higher if the EPA decides infants and children are more sensitive than adults.
         2. In the rest of the world, the WHO (World Health Organization) standard is used as the benchmark and is called the acceptable daily intake (ADI) rather than the RfD and for certain classes of compounds (especially the organophosphate insecticides) is quite different in quantity from the RfD (the ADI is sometimes a higher “permissible” exposure than the RfD).
      b. **The residues of pesticide on the commodity and how much of that commodity is consumed** (based on the USDA’s Continuing Survey of Food Intake by Individuals [CSFII], which is an empirical database of food consumption patterns).
         1. The average amount of a commodity consumed will be used in the first attempt at the TMRC analysis.

D. Assumptions (rules?) of the TMRC:
   1. Every acre of crops for which a pesticide is to be registered are treated with the maximum proposed application rate of the chemical;
a. The area of crops treated is known as the %CT (crops treated); for the TMRC or Tier I analysis it is assumed to be 100%, another very unlikely occurrence.
b. Note that for older compounds that have been commercially available for some time, the %CT on major field, fruit, and vegetable crops can be estimated from the NASS (USDA’s National Agricultural Statistical Service database (http://usda.mannlib.cornell.edu/reports/nassr/other/pnu-bb/)

2. Residues will be at the level of the proposed tolerance in every proposed commodity use (i.e., every crop use has to appear on a specific pesticide product’s label and therefore must have an associated pesticide residue tolerance; all of this is published in the Code of Federal Regulations in Parts 150-180);
a. Using a single value for the residue, i.e., the tolerance value, is called a deterministic analysis.
   1. In contrast, a probabilistic analysis would use the entire range of data (see below for further discussion).

3. The known food consumption patterns for individual commodities proposed under the registration is multiplied by the tolerance residues for that commodity and summed over all commodities proposed under the registration.

E. The TMRC actually represents the theoretical exposure to a person from dietary consumption of all commodities with the residue level at the tolerance level.
1. Ideally, the TMRC should not exceed the RfD;
2. When the TMRC does exceed the RfD, then the assessment may be refined by using field residues or other empirically determined residues (see below for dietary exposure assessment).
   a. Thus, note that a TMRC analysis does not really deal with the issue of risk until a detailed exposure analysis is conducted. In the absence of actual residue data, however, only tolerances can be used and the likelihood of exceeding the RfD becomes higher than when actual residue information are used.
   b. Indeed, EPA will use anticipated residue concentration (ARC) data if the TMRC analysis exceeds the RfD.
      1. Note that for newer lower toxicity compounds, the TMRC is not likely to exceed the RfD.
      2. Validation of tolerances for the older OPs, which are comparatively the most hazardous compounds from the perspective of acute toxicity (i.e., they tend to have low LD50 values), are likely to exceed the RfD by a TMRC analysis for two reasons.
         a. The RfDs for OP compounds are based on greater than or equal to 10% inhibition of either plasma cholinesterase (also known as pseudo cholinesterase or butyryl cholinesterase) or red blood cell acetylcholinesterase (the same enzyme as found in the central nervous system).
         b. Exposures are significantly lower, perhaps one or more orders of magnitude lower, than indicated by the tolerance level.

F. Example calculation of exposure under a TMRC scenario:
1. For example, the pesticide chlorpyrifos is used on numerous crops, but let’s pretend that apples and wheat make up the majority of uses; the tolerance that had been set for
apples prior to crop year 2000 was 1.5 µg pesticide/g apple (which is 1.5 mg/kg apple or 1.5 ppm), and for wheat it was set at 0.5 µg/g, (0.5 mg/kg).

2. Let’s pretend that the average male adult eats 100 grams per day of wheat and 75 grams per day of apples;

3. Assuming that chlorpyrifos is present at its full tolerance value, then

\[
\sum (1.5 \text{ µg/g x } 75 \text{ g/day}) + (0.5 \text{ µg/g x } 100 \text{ g/day}) = 162.5 \text{ µg/day} (0.1625 \text{ mg/d})
\]

Daily Consumption = \( \frac{162.5 \text{ µg/d}}{70 \text{ kg bw}} = 2.32 \text{ µg/kg bw/day} (0.00232 \text{ mg/kg}) \)

4. Thus, chlorpyrifos TMRC (in this case for only two commodities is 2.32 µg/kg bw/day, where bw = body weight of a typical adult male @ 70 kg.

5. The TMRC, expressed as µg pesticide residue /kg body weight/day (or mg/kg/day) ideally should not exceed the RfD
   a. The RfD for chronic exposure to chlorpyrifos is 0.3 µg/kg bw/day (0.0003 mg/kg/d);
   b. Thus, you can see that the exposure to chlorpyrifos based on worst-case assumptions exceeds the so-called safety benchmark.
   c. However, if real dietary exposure was used to calculate a modified TMRC, than estimated chronic exposure would be far different;
   d. For ex., the FDA has estimated that a 6-11 mo. old child consumes 0.015 µg/kg bw/d (Gunderson, 1995, JAOAC 78:1353); thus if the infant ate the same amount of food as the adult (I know that’s absurd), then 20 times less than the “safety” standard would be consumed.

G. For every crop/pesticide combination, the amounts consumed and pesticide residues (using the proposed tolerance level) are estimated; then all of this exposure is aggregated (added together); the sum of all the exposures for all uses should not exceed the RfD.

III. Are Tolerances Safety Standards?

A. Tolerances are not really safety standards in the strict sense of the meaning associated with the phrase “safety standard” because they are set artificially high to take into account agronomic practices without consideration of health (in other words, companies are determining how application practices, bad or good, might affect the distribution of residues, and then proposing tolerances to be above the extreme end of the range.)

1. For example, in the chlorpyrifos situation above, notice how the tolerance for applies had been set 3 times higher than for wheat; ironically we eat fresh applies in fairly large quantities, but wheat is likely to be baked into something else, affording the opportunity for dissipation or breakdown of residues. Thus, we can conclude that the 1.5 ppm tolerance set for applies recognizes the need for late (i.e., close to harvest) applications of chlorpyrifos and the inability to remove all the residues prior to harvest.

B. Furthermore, as you will see from a review of actual dietary intake, violation of a tolerance does not really mean an increased risk of injury because of the tremendous safety factors built into the RfD, on which the sum total of all tolerances are based; thus violation of a tolerance does not create an unsafe condition

1. However, in terms of the whole system of tolerance setting relative to a consideration of the RfD, I have argued that tolerances can be considered health based
a. All tolerances added together cannot exceed the RfD, which is a health based risk assessment estimate. Note that this argument is likely only applicable to new pesticides that have no history of market residues.
   1. Using the risk cup analogy, the maximum amount of risk is represented by the RfD; when the cup is full, no more risk is allowed; the cup is filled by exposures from diet, water, and residential residues.

C. If a manufacturer wants to register an older product for a new crop use, the proposed tolerance, when added together with all the other tolerances, must not exceed the RfD
   1. Thus, a manufacturer won’t support the registration on the nth crop if its proposed tolerance will cause the RfD to be exceeded by the TMRC.
   2. A manufacturer could petition, however, to have the tolerances lowered on another registered use so that when the new use is considered the TMRC won’t be exceeded.
   3. In reality, the analysis would not rely solely on the tolerance levels, but more likely on the anticipated residue concentrations.

IV. Dietary Exposure Assessment—Post FQPA
A. Recall that risk is a function of toxicity and exposure.
   1. Measures of toxicity, also known as endpoints (for example, the NOAEL), are determined from the myriad of required acute, short-term, subchronic, and chronic mammalian hazard identification and dose-response characterization studies.
   2. While the TMRC analysis is a first guess on whether a tolerance is appropriate or not, it does not say anything about actual exposure, nor risk (likelihood of harm) from a particular exposure.

B. For risk analysis, EPA considers two timeframes of exposure—acute exposure and chronic exposure.
   1. **Acute exposure** is assumed to be the maximum residues consumed during a 24 hour period.
      a. Or in other words, the acute exposure assessment assumes extremes in food consumption and in residue concentration.
      b. For acute dietary risk assessment, the entire distribution of single day food consumption events is combined with a distribution of residues (probabilistic analysis, referred to as "Monte Carlo") to obtain a distribution of exposures in mg/kg/day.
         1. EPA chooses the 99.9 percentile of exposure as its extreme end of the distribution.
            a. Thus, acute dietary exposure assessment is by definition a probabilistic exposure assessment.
   2. **Chronic exposure** is assumed to be the average residues consumed over a 70-year lifetime.
      a. EPA assumes average food consumption and average residues are eaten.
      b. The rationale is that over a life-time, a person tends toward the average in exposure.
      c. For chronic dietary risk assessments, the 3-day average of the consumption data for each sub-population is combined with average residues in commodities to determine the average exposure in mg/kg/day.
C. In assessing exposure to food residues, EPA uses a model known as **DEEM (Dietary Exposure Evaluation Model)**, which was developed by a consulting company called Novigen (Novigen was merged into the consulting firm Exponent).

1. All EPA has to do is plug in the distribution of food consumption data from the CFSII (which the model already contains) and the residue data (which can be the tolerance residues or refined data as is used in risk analysis for higher level Tiers. Thus, regardless of the pesticide under consideration food consumption patterns remain the same in the model. However, the residues will differ depending on the pesticide under consideration.

D. **The sources of residue data** beyond consideration of the tolerance concentration included the following:

1. Use of the maximum residues found in manufacturer field trials;
2. Use the field residues at the 95\textsuperscript{th} percentile;
3. Use the average residues;
4. Rely on government surveillance and dietary monitoring programs (see discussion of these programs below).

   a. One set of programs is conducted by the Food & Drug Administration (FDA) [Surveillance and Monitoring Program and their Total Diet Study program];
   b. Another program is the USDA Pesticide Data Program

5. Market basket surveys (usually industry sponsored);

   a. These programs collect samples of food from the market place (retail groceries, for example) in representative U.S. cities and then conduct residues analysis.
   b. Advantages of real residue data are shown in the graph below (Figure 2, modified from Wright 1999, DowAgro).

   1. The y-axis is the residue concentration for the OP insecticide chlorpyrifos, and the x-axis is the cumulative frequency of occurrence.

   a. In other words, for the farm gate residues reflecting percent crop treated (triangle line), about 99\% of all residue detections were \(~1.1\) ppm chlorpyrifos or less.
   b. For the market basket survey study, residues at the 99\textsuperscript{th} percentile were well under 0.1 ppm.

![Figure 2](http://vm.cfsan.fda.gov/~lrd/pestadd.html)

Figure 2. Cumulative frequency of occurrence of chlorpyrifos residues (mg/kg) in a market basket sample of fresh produce. Note the greater frequency of residues above 0.1 ppm in produce sampled at the “farm gate” (i.e., at the field level) than residues from produce in retail stores.
E. **Consumption Data** are an integral part of exposure assessment

1. As mentioned previously, the source of the consumption data is the USDA CSFII database, which is updated every few years.
   a. In the survey, the USDA researchers "follow a person around" for three days. Actually, the "volunteer" records everything they eat and preserves half of it for weighing. Each day of observation is called a person-day.
   b. Subgroups are based on age so that USDA can figure out what an infant consumes, a 1-6 year old consumes, etc.
   c. For composite foods, for example, pizza, and processed, blended foods, a "map" exists for deconvoluting the foods into the commodities for which tolerances exist.
      1. For example, pizza contains X grams of tomatoes, X grams of wheat, etc.
   d. Dividing the mass of food consumed on one day by the weight of an average person in each subgroup (for example, adult male, 70 kg; adult female, 60 kg; or child, 10 kg) gives the grams of food consumed per kg body weight per day, which can also be expressed as kg food/kg body weight.
      1. Thus, the CSFII takes into account consumption patterns that are unique to each subpopulation group as well as normalizing consumption to average body weight for that group.

F. For **chronic exposure assessment**, EPA only needs to know the average consumption values for each food among each population subgroup. Also, the average residues can be used.

1. Then, DEEM multiplies each combination of average food consumption and average residues to obtain exposure and then sums up the exposures over all foods to derive the chronic dietary exposure value for each subpopulation.

G. For **acute exposure assessment**, EPA employs a probabilistic technique known as Monte Carlo analysis, where the entire distribution of food consumption values and residue values are used. Essentially the distributions are multiplied together (Figure 3).

1. DEEM can estimate the distribution of exposures using the Monte Carlo technique, and then the percentile of exposure can be calculated for each population subgroup.
2. Recall that for acute exposure assessment, EPA is interested in the 99.9\(^{th}\) percentile of dietary exposure.

H. Hypothetical example of how a probabilistic acute dietary exposure assessment works.

1. Consider the following two tables showing hypothetical consumption data from the USDA CSFII database and hypothetical data for chlorpyrifos residues from the USDA PDP.

Table 1. Hypothetical data food consumption data (as kilograms of food consumed per day) from the USDA CSFII database.

<table>
<thead>
<tr>
<th>Food matrix</th>
<th>Person 1 Day 1</th>
<th>Person 1 Day 2</th>
<th>Person 1 Day 3</th>
<th>Person 2 Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>0.100</td>
<td>0.150</td>
<td>0.000</td>
<td>0.050</td>
</tr>
<tr>
<td>Peach</td>
<td>0.020</td>
<td>0.100</td>
<td>0.000</td>
<td>0.100</td>
</tr>
<tr>
<td>Raisins</td>
<td>0.030</td>
<td>0.050</td>
<td>0.010</td>
<td>0.000</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>0.000</td>
<td>0.750</td>
<td>0.040</td>
<td>0.100</td>
</tr>
<tr>
<td>Pizza</td>
<td>0.060</td>
<td>0.000</td>
<td>0.050</td>
<td>0.200</td>
</tr>
<tr>
<td>Cookies</td>
<td>0.040</td>
<td>0.060</td>
<td>0.040</td>
<td>0.030</td>
</tr>
<tr>
<td>Granola Bar</td>
<td>0.020</td>
<td>0.030</td>
<td>0.060</td>
<td>0.015</td>
</tr>
<tr>
<td>Hot Dog</td>
<td>0.075</td>
<td>0.075</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>French Fries</td>
<td>0.080</td>
<td>0.060</td>
<td>0.040</td>
<td>0.000</td>
</tr>
<tr>
<td>Milk</td>
<td>0.060</td>
<td>0.200</td>
<td>0.100</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Table 2. Hypothetical chlorpyrifos residues (mg/kg) on various food items in the USDA PDP database. Note that items like pizza and cookies have been determined by deconvoluting the actual constituent ingredients for which there is a crop tolerance (this illustration then shows the total residue as the sum of all the residues in the individual ingredients).

<table>
<thead>
<tr>
<th>Food matrix</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
<th>Sample 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>0.003</td>
<td>0.054</td>
<td>0.023</td>
<td>0.002*</td>
</tr>
<tr>
<td>Peach</td>
<td>0.010</td>
<td>0.02</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Raisins</td>
<td>0.030</td>
<td>0.005</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>0.002</td>
<td>0.015</td>
<td>0.040</td>
<td>0.002</td>
</tr>
<tr>
<td>Pizza</td>
<td>0.060</td>
<td>0.000</td>
<td>0.050</td>
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<tr>
<td>Cookies</td>
<td>0.002</td>
<td>0.002</td>
<td>0.010</td>
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<td>0.002</td>
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<td>0.002</td>
</tr>
<tr>
<td>French Fries</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Milk</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Note that zero residues are not shown. As policy, the EPA chooses to consider a non-detect as a quantity equal to one-half of the analytical detection level. Thus, if the detection limit is 0.003 ppm, than one half of the detection limit is 0.0015 ppm (which is 0.002 ppm based on three significant figures).
2. Exposure is derived by multiplying the consumption level for each commodity by the residue for that commodity. Note that in the tables above, the residues are shown for pizza, corn flakes, etc., but for convenience the residue values represent the sum of the levels found in the individual foods.

a. If all the residues and food items were being used, then the exposure could easily be determined using matrix algebra as shown below (Figure 4).

1. Note that in this example, the body weight is not shown (for convenience); the exposure, however, would be expressed on a body weight basis (typically 70 kg and 60 kg for male and female, respectively, and 10 kg for a child).

2. The “food consumed” and “pesticide residue” shown below are the lines for apple and peach from table 1 and table 2, respectively.

![Figure 4. Schematic example of how the combination of food consumption and residue data are multiplied to yield exposure. In the scheme above, all data is used, but in the Monte Carlo analysis, the consumption and residue databases are randomly sampled over and over again to yield a probabilistic distribution of exposures.](image)

b. In the Monte Carlo analysis, the computer program randomly selects a consumption level for each food item and matches it to a randomly selected residue value.

1. The random sampling process for each food can be repeated for hundreds of iterations until a stable distribution of exposures to that food item are derived.

2. Once one food’s exposure distribution is derived, then the computer program moves on to the next food item.

3. The total exposure to all foods are simply the sum of the individual exposures for each food item over all iterations.

3. The EPA then plots the distribution of probabilistic exposures for each age group; they are interested in consumption of pesticide residues at the 99.9th percentile of exposure.
a. Thus, exposure at the 99.9\textsuperscript{th} percentile means that only 0.1\% of the population has exposure greater than the stated exposure level.

a. For example, if the 99.9\textsuperscript{th} percentile exposure is 0.000015 mg/kg/day, than 0.1\% of the population may have an exposure greater than 0.000015 mg/kg/day; alternatively 99.9\% of the population has exposure equal to or less than 0.000015 mg/kg/day.

4. There are some statistical problems with the validity of using a 99.9\textsuperscript{th} percentile exposure as shown by the large uncertainty (given as 95\% confidence intervals) around the estimate of exposure at this level (Figure 5).

a. The statistically associated flaws, which tend toward an overestimation of exposure at the 99.9\textsuperscript{th} percentile, were also documented by Chaisson et al. 1999. Overestimation Bias and Other Pitfalls Associated with the Estimated 99.9th Percentile in Acute Dietary Exposure Assessments. Regulatory Toxicology and Pharmacology 29:102-127.

![Figure 5](image_url)

Figure 5. Uncertainty in consumption estimates at different percentiles of the population (based on a probabilistic food consumption analysis (Chaisson et al. 1999)).

V. Dietary Risk Characterization

A. Once the 99.9\textsuperscript{th} percentile of exposure for the acute exposure characterization and the average exposure for the chronic exposure characterization are determined, they are divided by either the RfD (NOAEL divided by 100) or the Population Adjusted Dose (PAD; the RfD divided by 10, which is considered the FQPA specific safety factor for protecting children).

1. For each type of exposure timeframe, chronic or acute, the RfD and PAD may be different.
   a. Usually, the acute endpoints are larger than the chronic, mainly because exposure is shorter and there has been no opportunity for cumulative toxic effects.

2. The acute risk benchmarks are designated as aRfD or aPAD; the chronic benchmarks are designated as cRfD or cPAD.

B. EPA has been especially interested in OP insecticides and acute dietary exposure risk;

1. Current estimates of acute dietary exposure often fail to meet the safety benchmarks.

2. Most notable have been the OP insecticides methyl parathion, azinphos-methyl, and chlorpyrifos.
3. To determine the safety benchmark, all exposures are thrown into the risk cup; exceedance of the risk cup occurs when exposure is >100% of the RfD or PAD.
   a. Thus, when exposure is greater than 100% of the RfD or PAD, EPA characterizes the risk as exceeding their Levels of Concern (LOC).

C. Case Study—Azinphos-methyl (AZM) and Methyl Parathion (MP)
   1. OP insecticides are the most hazardous of pesticides by virtue of their ability to inhibit cholinesterase at comparatively low dosages yet cause no overt signs of toxicity.
      a. EPA prioritized assessment of the OPs first among other pesticides in implementing the provisions of the FQPA.
   2. Two OPs in particular, AZM and MP are good examples of dietary risk assessment that allows a comparison of what happens when the toxicological endpoints are affected by the extra 10X FQPA safety factor (as it was for MP), and the risk management decision to cancel a compound (i.e., MP) on certain crops when alternatives are available.
      a. The acute and chronic toxicological endpoints for both AZM and MP were determined in typical mammalian toxicity studies on rats. The most sensitive endpoint was cholinesterase inhibition, as it is for nearly all of the OP insecticides (Table 3).
         1. Thus, the most sensitive endpoint will be the pathological, physiological, or biochemical effect exhibiting the lowest NOAEL.

Table 3. Acute and chronic toxicological endpoints for AZM and MP (dosages expressed as mg/kg/day).

<table>
<thead>
<tr>
<th>Toxicological Endpoints</th>
<th>Azinphos-methyl</th>
<th>Methyl Parathion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Oral LD50</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Acute Dermal LD50</td>
<td>2000</td>
<td>6</td>
</tr>
<tr>
<td>Acute NOEL</td>
<td>0.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Chronic NOEL</td>
<td>0.149</td>
<td>0.02</td>
</tr>
</tbody>
</table>

b. Table 4 represents the risk characterization parameters, the RfD and the PAD.
   1. Note that methyl parathion has a PAD different from the RfD, whereas the PAD for azinphos-methyl is the same as its RfD.
   2. EPA determined that several published studies suggested that MP was more toxic to neonatal rats on a body weight basis than it was to adult rats.
      a. In another words, neonatal rats were more susceptible to a given dosage (mg/kg/day) than the female parent was.
      b. Studies submitted by the manufacturer under EPA’s testing guidelines showed no differential sensitivity between neonatal and parent rats.

Table 4. Risk characterization endpoints for AZM and MP.

<table>
<thead>
<tr>
<th>Risk Characterization Endpoints</th>
<th>Azinphos-methyl</th>
<th>Methyl Parathion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Reference Dose</td>
<td>0.003</td>
<td>0.0011</td>
</tr>
<tr>
<td>Acute Population Adjusted Dose</td>
<td>0.003</td>
<td>0.00011</td>
</tr>
<tr>
<td>Chronic Reference Dose</td>
<td>0.00149</td>
<td>0.0002</td>
</tr>
<tr>
<td>Chronic Population Adjusted Dose</td>
<td>0.00149</td>
<td>0.00002</td>
</tr>
</tbody>
</table>
3. Table 5 presents the dietary risk characterization for methyl parathion with consideration of all foods with tolerances.
   a. Note that under the heading “pre-mitigation”, methyl parathion significantly exceeded the aPAD.
   b. After apples, peaches, pears, and grapes were removed from consideration, methyl parathion was below the LOC (i.e., the % aPAD was less than 100).

Table 5. Dietary risk characterization for methyl parathion before mitigation and after mitigation of exposure to certain foods.

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Methyl Parathion Pre-Mitigation</th>
<th>Methyl Parathion Post Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposure (mg/kg/day)</td>
<td>% aPAD</td>
</tr>
<tr>
<td>U.S. Population</td>
<td>0.000416</td>
<td>378</td>
</tr>
<tr>
<td>All infants &lt; 1 yr</td>
<td>0.000415</td>
<td>377</td>
</tr>
<tr>
<td>Children 1-6 yrs</td>
<td>0.000969</td>
<td>881</td>
</tr>
<tr>
<td>Children 7-12 yrs</td>
<td>0.000428</td>
<td>388</td>
</tr>
</tbody>
</table>

4. AZM dietary risk characterization using a number of residue values at the tolerance yielded exposure above the RfD (Table 6).
   a. Refinement of the assessment to include field residues and USDA PDP data significantly lowered the estimated risk.

Table 6. Dietary risk characterization of azinphos-methyl before and after residue refinement to reflect real world exposures.

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>AZM Not Refined</th>
<th>AZM Refined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposure mg/kg/day</td>
<td>% aRfD</td>
</tr>
<tr>
<td>U.S. Population</td>
<td>0.005519</td>
<td>85</td>
</tr>
<tr>
<td>All infants &lt; 1 yr</td>
<td>0.009934</td>
<td>331</td>
</tr>
<tr>
<td>Children 1-6 yrs</td>
<td>0.010343</td>
<td>202</td>
</tr>
<tr>
<td>Children 7-12 yrs</td>
<td>0.006556</td>
<td>129</td>
</tr>
</tbody>
</table>

D. Note that there were no concerns over chronic exposure; all risk estimates were below the cPAD.
E. The bottom line in assessing food residue concerns is not really one of whether or not pesticide residues are in or on crops because indeed they are! The question is exposure and how much (i.e., dietary intake).

VI. Drinking Water Exposure and Risk Assessment
A. EPA aggregates drinking water and residential exposure; for both MP and AZM there is no residential uses, and thus exposure is likely to only occur from food and drinking water.
   1. Ideally, aggregate risk assessment would have enough empirical data to conduct a probabilistic assessment so that an overall distribution of exposures is obtained as illustrated in Figure 6.
Probabilistic Aggregate Exposure Assessment

Figure 6. Hypothetical probabilistic aggregate exposure assessment where distributions of dietary (including drinking water) and residential exposure are considered. The curves represent the frequency that a particular exposure occurs in one day. All the frequency curves are then added to aggregate the total exposure for all days of use.

B. For drinking water exposure, the EPA does not calculate the level of exposure.
   1. Rather, the agency calculates a DWLOC, or drinking water level of comparison.
      a. The DWLOC represents the level in water, accounting for dietary exposure, that can be consumed without exceeding the RfD or PAD.
         1. The DWLOC is determined for both acute and chronic exposure scenarios using the following formula.

\[
DWLOC (\mu g/L) = \frac{\text{chronic water exposure (mg/kg/d)} \times \text{body weight (kg)}}{\text{consumption (L/d)} \times 10^{-3} \text{mg/\mu g}}
\]

where chronic water exposure (mg/kg/d) = [PAD – food exposure (mg/kg/d)]

C. The residues in drinking water are estimated by EPA by using a combination of several pesticide behavior computer simulation models.
   a. Drinking water is derived from surface water and ground water resources.
   b. Residues in surface water are modeled using PRZM v. 3 (Pesticide Root Zone Model), which estimates residues leaving the field edge in runoff and erosion.
      1. Once the pesticide is in the surface water, its behavior (namely its half-life) is modeled using EXAMS (Exposure Analysis Modeling System).

D. Case Study—Methyl Parathion
   1. Prior to mitigating the acute dietary exposure and risk for MP, the DWLOC was considered zero because the aPAD was already exceeded.
   2. However, after mitigation, the acute DWLOC was calculated as shown in Table 7.
      a. Note that the volume consumed varies by age group:
1. For adults, 2 L are assumed; for children, 1 L is assumed.
2. Body weights are 70 kg for males, 60 kg for females, 10 kg for children.
3. Note that the DWLOC for adults exceeded the monitoring data, indicating that there should be “excess” risk from exposure of MP in drinking water.
   a. However, for infants and children, the DWLOC was either at or below the monitoring data, raising EPA concerns of “excessive” exposure.
   b. Note that the monitoring data represent an extreme. MP is hardly ever found in surface water, yet alone drinking water.
3. For chronic exposure, the DWLOCs were all above the monitoring data, so EPA was not concerned about excessive exposure.
4. Caveats—What Do the Monitoring Data Represent?
   a. The monitoring data shown in Tables 7 and 8 actually come from one place, Jefferson Parish, LA. Raw water samples from the Mississippi River were collected weekly over a year. MP was detected in 40% of the samples with an average of 0.009 µg/L and a high value of 0.041 µg/L.
   1. Note that in Table 7, which comes from EPA’s revised human health risk assessment, the number was denoted as 0.42, an obvious discrepancy from what was reported in EPA’s Ecological Fate and Effects Division assessment that described the Jefferson Parish sampling.

Table 7. Aggregate acute exposure and risk assessment for MP after mitigation (removal of uses on apples, pears, peaches, and grapes.)

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Water Monitoring Data (µg/L)</th>
<th>aPAD (mg/kg/d)</th>
<th>Acute Food Exposure (mg/kg/d)</th>
<th>Acute Water Exposure (mg/kg/d)</th>
<th>DWLOC (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Male</td>
<td>0.42</td>
<td>0.00011</td>
<td>0.000067</td>
<td>0.000043</td>
<td>1.51</td>
</tr>
<tr>
<td>Adult Female</td>
<td>0.42</td>
<td>0.00011</td>
<td>0.000075</td>
<td>0.000035</td>
<td>1.05</td>
</tr>
<tr>
<td>Infants &lt;1 yr</td>
<td>0.42</td>
<td>0.00011</td>
<td>0.000067</td>
<td>0.000043</td>
<td>0.43</td>
</tr>
<tr>
<td>Children 1-6</td>
<td>0.42</td>
<td>0.00011</td>
<td>0.000087</td>
<td>0.000023</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Table 8. Chronic exposure and risk assessment for MP after mitigation (removal of uses on apples, pears, peaches, and grapes.)

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Water Monitoring Data (µg/L)</th>
<th>aPAD (mg/kg/d)</th>
<th>Acute Food Exposure (mg/kg/d)</th>
<th>Acute Water Exposure (mg/kg/d)</th>
<th>DWLOC (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Male</td>
<td>0.009</td>
<td>0.00002</td>
<td>0.000002</td>
<td>0.000018</td>
<td>0.63</td>
</tr>
<tr>
<td>Adult Female</td>
<td>0.009</td>
<td>0.00002</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>0.00002</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>0.00002</td>
<td>0.000009</td>
<td>0.000011</td>
<td>0.11</td>
</tr>
</tbody>
</table>

2. However, the USGS, through its NAWQA program (the National Water Quality Assessment program, [http://water.usgs.gov/nawqa/nawqa_home.html](http://water.usgs.gov/nawqa/nawqa_home.html)) reported for 1996-97 monitoring a low of 0.015 µg/L and a high of 0.422 µg/L.
a. Thus, you can see how EPA selects data at the extremes when it does a risk assessment.
b. In the absence of specific monitoring data, such as available through the USGS NAWQA database or municipal monitoring (which is required under the Safe Drinking Water Act), EPA will default to models as previously indicated. Table 9 shows what the modeled values of MP in water would have been using the PRZM 3 computer simulation.

<table>
<thead>
<tr>
<th>Crop</th>
<th>Maximum µg/L</th>
<th>4-Day µg/L</th>
<th>21-Day µg/L</th>
<th>60-Day µg/L</th>
<th>90-Day µg/L</th>
<th>Long-Term Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton</td>
<td>254.4</td>
<td>174.2</td>
<td>70.6</td>
<td>32.8</td>
<td>23.2</td>
<td>6.6</td>
</tr>
<tr>
<td>Corn</td>
<td>39.5</td>
<td>27.3</td>
<td>12.2</td>
<td>5.4</td>
<td>3.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Alfalfa</td>
<td>4.3</td>
<td>2.9</td>
<td>1.4</td>
<td>0.8</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Potato</td>
<td>21.3</td>
<td>14.3</td>
<td>6.7</td>
<td>3.7</td>
<td>2.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Pecan</td>
<td>12.3</td>
<td>9.4</td>
<td>6.0</td>
<td>3.7</td>
<td>3.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Sweet Potat</td>
<td>36.4</td>
<td>24.8</td>
<td>10.8</td>
<td>5.7</td>
<td>4.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Table 9. 90th Percentile EECs (estimated environmental concentrations) for methyl parathion is surface water for simulated crop scenarios.

VII. Residential Exposure Assessment
A. Very few studies of exposure at residential sites have been carried out. In the absence of actual data, estimated exposures are developed using assumptions about application, area treated, rates of application, body surface areas, durations of exposure, and transfer efficiency (i.e., the transfer to the skin of residues lying on a surface.
1. The EPA has developed a set of Standard Operating Procedures (SOPs) for conducting residential exposure assessments in the absence of having empirical studies.

B. Some key assumptions in the EPA SOPs for Residential Exposure Assessments
1. First, exposure for residents is considered short term (acute) or at most intermediate term.
2. The label (current or proposed) of the registered product gives information on application rates and product active ingredient per unit of finished spray (or per unit of weight if granular materials are used).
3. Information about body surface area and weights comes from the EPA Exposures Factor Handbook

C. Basic Formulas (selected examples) for calculating residential exposure
1. \[ \text{PDR} = \text{UE} \times \text{AR} \times \text{A} \]
   a. PDR = potential dose rate (mg/day);
   b. UE = unit exposure (mg/lb ai);
   c. AR = application rate (lb ai/acre or lb ai/gal);
   d. A = area treated (acres/day or gal/day);
   e. ai = active ingredient.
2. The PDR is changed to an exposure (mg/kg/day) by dividing by the appropriate body weight (BW).
   a. \[ \text{PDR(normalized for body weight)} = \frac{\text{PDR}}{\text{BW}} \]
3. Note that besides the routine application information needed to conduct the assessment, the UE is a key to estimating potential dose.
a. EPA has estimated standard unit exposures for inhalation and dermal doses (the main routes of residential exposure, unless children are ingesting soil or engaging in hand-to-mouth behavior).

b. For lawn applications of granulars and liquids, the unit exposure for inhalation and dermal routes has been estimated by EPA to be 3.0 mg/lb of active ingredient.
   1. Other generic factors are 0.5 acres treated per day.

4. Example calculation for lawn treatment with a granular product (for example, fertilizer impregnated with the herbicide 2,4-D)
   a. Note that for granular materials only be dermal exposure would be assumed.
   b. The scenario assumes an application rate of 1 lb ai/acre and an adult making the application (BW = 71.8 kg).
   c. PDR(normalized to BW) = (UE x AR x A)/BW
      1. PDR (mg/kg/day) = (3.0 mg/lb ai x 1 lb ai/acre x 0.5 acre/day)/71.8 kg = 0.02 mg/kg/day

5. For post application exposure, the dermal transfer coefficient is needed plus an assumption of how much residue is available for transfer to the skin.
   a. For example, for turf grass, it may be assumed that 20% of the application rate is available from the turfgrass as dislodgeable residues on the day of application. The DFR (dislodgeable foliar residue) is estimated as the amount of residues that can be extracted from a leaf using a combination of water and surfactant. These data come from studies of DFR that companies are required to submit in support of worker exposure assessments.
   b. It is assumed that the pesticide handler is exposed on the day of application. For exposure beyond the day of application, a pesticide dissipation rate is needed.
   c. The upper percentile dermal transfer coefficient is assumed to be 43,000 cm²/hr for adults and 8,700 cm²/hr for toddlers.
      1. The dermal transfer coefficient represents the total surface area equivalents of skin exposed during a unit time (one hour) of exposure.
      2. For example, 43,000 cm² per hour represents how much equivalent surface area a pesticide handler would be exposed to based on repeated surface area contact during one hour intervals. Infants are smaller than adults so less surface area is exposed during one hour.
         a. Bear in mind that although less surface area of an infant is exposed than the surface area of an adult, the body weight of the infant is much smaller so the effective dose could be higher.
         b. The duration of exposure for adults and toddlers (95th percentile)O is assumed to be 2 hours per day.
   d. The formula is PDRt = DFR x CF1 x Tc x ET, where
      1. PDRt = potential dose rate on day “t” (mg/day);
      2. DFRt = dislodgeable foliar residue on day “t” (µg/cm²);
         a. DFRt = AR x F x (1-D)t x CF2 x CF3, where
            1. AR = application rate (lbs ai/ft² or lb ai/acre)
            2. F = fraction of ai retained on foliage (unitless)
            3. D = fraction of residue that dissipates daily (unitless)
            4. t = post application day on which exposure is being assessed
            5. CF2 = weight unit conversion factor to convert the lbs ai in the application rate to µg for the DFR value (4.54E08 µg/lb);
6. CF3 = area unit conversion factor to covert the surface area units (ft²) in the application rate to cm² for the DFR value (1.03E-03 ft²/cm² or 24.7E-09 acre/cm² if the application rate is per acre).

3. CF1 = weight unit conversion factor to convert µg units in the DFR value to mg for the daily dose (0.001 mg/µg);

4. Tc = transfer coefficient (cm²/hr);

5. ET = exposure time (hr/day)

6. The PDR would be divided by the body weight to obtain exposure (mg/kg/day)

e. Example calculation for post application exposure from a 2.2E-05 lbs ai/ft² (about 1 lb ai/acre) application rate.

1. \[ \text{DFR}_0 = \text{AR} \times F \times (1-D)^t \times \text{CF2} \times \text{CF3} \] (DFR on day 0);
   a. \[ \text{DFR} = 2.2E-05 \text{ lb ai/ft}^2 \times 0.2 \times (1-D)^0 \times 4.45E08 \text{ µg/lb} \times 1.08E-03 \text{ ft}^2/\text{cm}^2 \]
   1. \[ \text{DFR}_0 = 2.16 \text{ µg/cm}^2 \]
   b. \[ \text{PDR}_0 = \text{DFR}_0 \times \text{CF1} \times \text{Tc} \times \text{ET} \]
      1. \[ \text{PDR}_0 = 2.16 \text{ g/cm}^2 \times 0.001 \text{ mg/µg} \times 8,700 \text{ cm}^2/\text{hr} \times 2 \text{ hr/day} \]
      2. \[ \text{PDR}_0 = 37.6 \text{ mg/day} \]
   2. \[ \text{PDR (normalized to BW)} = (37.6 \text{ mg/day})/(15 \text{ kg assumed weight of toddler}) = 2.51 \text{ mg/kg/day} \]

D. The potential dose rates can be modified by dermal absorption efficiency (for example is only 3% of dose is absorbed, than the PDR would be multiplied by 0.03).

1. The resulting dosage is added to the acute dietary exposure to determine the aggregate exposure.
   a. Note that the drinking water exposure could also be added, but the EPA prefers to calculate a DWLOC and then compare that number to either monitored or modeled water residue data (note that the 90th percentile or above data from monitoring or computer simulations are used).

VIII. Case Study of FQPA Aggregate Risk Assessment—The Chlorpyrifos Risk Assessment

A. Of all the OP risk assessments, the one for chlorpyrifos is the richest in terms of having empirical data.

1. Dow AgroSciences (DAS), the manufacturer of chlorpyrifos (sold as Dursban in the urban market and as Lorsban in the agricultural market) has probably collected more dietary, drinking water, and residential exposure data on their compound than any other manufacturer has done for their compound.
   a. Furthermore, DAS has published for chlorpyrifos more toxicological information (hazard identification information) and risk characterization information in the refereed published literature than is available for any other pesticide.

B. To make a long story short, chlorpyrifos is one of the few OP insecticide for which EPA determined there is a special children’s sensitivity concern, and therefore an FQPA 10X extra safety factor was applied in the risk characterization. For more details see my essays at [www.tricity.wsu.edu/aenews](http://www.tricity.wsu.edu/aenews)


C. First, note the toxicological endpoints and risk characterization parameters for chlorpyrifos (Table 10).
1. When EPA does a risk assessment under the FQPA, it will first release a draft RED. It will then take comments and revise it.
2. Note that for chlorpyrifos, the EPA became even more conservative on its risk assessment.

Table 10. Toxicological endpoints and “safe” levels (mg/kg/day) of chlorpyrifos exposure.

<table>
<thead>
<tr>
<th>Toxicological Parameter</th>
<th>Preliminary Risk Assessment</th>
<th>Revised Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>LOEL</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>NOEL</td>
<td>0.5</td>
<td>0.03</td>
</tr>
<tr>
<td>RfD</td>
<td>0.005</td>
<td>0.0003</td>
</tr>
<tr>
<td>PAD</td>
<td>0.0017</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

LOEL = lowest dose causing cholinesterase enzyme inhibition (lowest observable effect level); NOEL = dose causing no adverse effects; RfD = NOEL/100
Preliminary PAD = RfD/3; Revised PAD = RfD/10

D. In Figure 7 below, note that the acute dietary exposure of chlorpyrifos exceeds EPA’s levels of concern when its revised PAD is used.

**Chlorpyrifos Acute Dietary Risk Characterization**
Figure 7. Acute dietary risk characterization for chlorpyrifos showing exposure relative to the acute NOEL, the preliminary acute PAD, and the revised PAD. Exposure is shown for pre- and post mitigation of exposure analysis. The USDA single serving apple graphic used single apple residue sample (as opposed to composite apple samples). The Dow data-decomposition graphic was a statistical analysis to change composite residue data on fresh produce to single unit (or serving) data.

E. In the chlorpyrifos RA, EPA used models to estimate the residues of chlorpyrifos in drinking water (EECs) (Table 11), but then used data from the USGS NAWQA for risk characterization.

1. For risk from exposure to pesticide residues in water, EPA uses a DWLOC (Drinking Water Level of Concern) Approach (Table 11).
2. In this analysis, EPA calculates the level of pesticide residues in drinking water that would “match” the RfD or PAD
   a. Note that the daily consumption of water is based on 2 L for an adult and 1 L for a child
   b. When the acute dietary or residential exposure exceeds the RfD or PAD, EPA will still calculate a DWLOC, but the agency won’t use it to make a risk management decision.
3. Note that in the USGS NAWQA studies, the 95th percentile for chlorpyrifos in integrator surface water systems (the bigger rivers more likely to be the sources of drinking water) is 0.019 ppb with a maximum concentration detected (i.e., the 100th percentile) of 0.13 ppb (NAWQA studies).
4. For ground water (all stations sampled in NAWQA), the 95th percentile residue is <MDL (method detection level, 0.001 ppb) and the maximum concentration detected was 0.026 ppb.
   a. Thus, the USGS data shows lower concentrations of chlorpyrifos in water at the high end than the models estimate.

Table 11. Estimated environmental concentrations of chlorpyrifos in drinking water and EPA’s drinking water levels of comparison (DWLOCs).

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Surface Water EEC (µg/L)</th>
<th>Ground Water EEC (µg/L)</th>
<th>Acute DWLOC (µg/L)</th>
<th>Chronic DWLOC (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>0.026 – 0.4 chronic - acute</td>
<td>0.007 – 0.103 chronic – acute</td>
<td>166</td>
<td>10</td>
</tr>
<tr>
<td>Infants (&lt;1 yr)</td>
<td></td>
<td></td>
<td>2.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Children (1-6 yr)</td>
<td></td>
<td></td>
<td>0.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Females (13-adult)</td>
<td></td>
<td></td>
<td>9</td>
<td>0.72</td>
</tr>
</tbody>
</table>

F. DAS had conducted several studies for residential exposure. Figure 8 shows the exposure measured in persons exposed to a granular or spray Dursban application on a lawn (handler exposure).
Figure 8. Residential exposure on the day of application to a homeowner applying either granular or sprayed Dursban to a lawn.

1. Note that all exposure scenarios exceed the revised acute PAD. As a result, it was not necessary for EPA to even aggregate the residential exposures to dietary or drinking water exposure because this residential scenario alone exceeded their levels of concern.

**CUMULATIVE EXPOSURE ASSESSMENT & RISK CHARACTERIZATION**

**IX. Background Information for Cumulative Exposure & Risk Assessment**

A. The FQPA mandates EPA to cumulate exposures to pesticides whose mode of action are identical.

1. The rationale for exposure “cumulation” is that multiple pesticide residues could appear in a commodity, and some of these residues will be pesticides with identical modes of action.

   a. Note that the concern is not a synergistic response but rather an additive response.

   b. The rationale assumes that even if there is no response at the real world levels of exposure, it is possible that residues added together might be sufficient to cause a response.

1. However, this rationale ignores the fact that residues on food are so far below any NOEL that even adding them together is not likely to approached the NOEL.

2. Nevertheless EPA has embarked on a cumulative exposure assessment exercise examining all dietary exposure, drinking water exposure, and residential exposure for 24 OP insecticides.

   a. Note that the first step was actually to determine which groups of compounds had identical modes of action for all practical purposes.
1. The OP insecticides were assessed and determined to meet this standard. An independent analysis of the similarity in MOA was published:


X. Determination of Relative Potency Factors (RPFs) for Cumulative Exposure Assessment

A. In the cumulative exposure assessment and risk characterization, multiple residues of OP insecticides have to cumulated.

1. However, we cannot simply add residues together because each OP has a different potency for inhibition of acetylcholinesterase, the most sensitive toxicological endpoint upon which to determine risk of adverse effects.

2. To solve this problem, EPA determined the relative potency of the different OP insecticides, and from this calculated a relative potency factor (RPF) that would allow all residues to be converted to equivalents of one index OP (which was methamidophos).

3. RPFs are based on mode of exposure: oral, dermal, inhalational (note that the latter two pathways were treated the same).

B. EPA released a draft Cumulative Risk Assessment (CRA) during July 2001 and a revised CRA during June 2002.

1. Relative potency factors (RPFs) were revised using new acetylcholinesterase activity endpoints.

C. Oral Exposure route

1. In the older CRA (Cumulative Risk Assessment) from July 2001, the male RBC (red blood cell) acetylcholinesterase activity was used as the toxicological endpoint.

   a. “It was stated in that document that the RBC RPFs proved to be a reliable and sensitive endpoint considered protective of both the peripheral and central nervous systems for the majority of the chemicals. The major advantage of the RBC database was its large size compared to the whole brain ChE database; this large database allowed the examination of time course information and observation of a steady state response.”

2. In the revised CRA (from June 2002), female brain AChE was used. Reasons for the change in endpoints:

   a. “Principally, compared to relative potency estimates based on RBC, estimates of relative potency based on brain ChE have tighter confidence intervals and therefore will confer less uncertainty on cumulative risk estimates.

   b. “Also, these data represent a direct measure of the common mechanism of toxicity as opposed to using surrogate measures. The toxic potencies and PODs [points of departure] for brain cholinesterase inhibition for these OPs are generally similar to the RBC data for the oral, inhalation, and dermal exposures (USEPA, 2001b).”

   c. “Finally, in the present analysis, although male and female rats were equally sensitive for 30 OPs, female rats were more sensitive to three OPs. Therefore, OPP [EPA’s Office of Pesticide Programs] has chosen to base its RPFs on female brain measurements.”

3. Modeling of dose-response function for oral exposures resulting in AChE inhibition
a. EPA used an exponential model (called the basic model)
   1. The model is essentially a function that describes dose-response relationship for increasing brain AChE inhibition with increasing doses (Figure 9).

![Figure 9. Basic exponential model for determining the BMD10 from the dose-response function for female brain acetylcholinesterase inhibition.](image)

b. When the low doses gave a flat response (i.e., there was no measurable inhibition), then a modified model was used that relied on an estimation of internal dose. This model was called the expanded model. In Figure 10 below, you can see the results of modeling using the basic exponential model (the curve farthest to the left on the axes) and the expanded model (the curves further to the right).

![Figure 10. Output from the use of the expanded exponential model to account for low doses not causing any acetylcholinesterase inhibition.](image)
4. “Potency determinations of the OPs for the oral route exposure are based on the benchmark dose where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). The BMD_{10} was selected as the effect level for potency determination because this level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to the background cholinesterase.”

D. Dermal and Inhalational Routes
1. When an OP has residential use, dermal and inhalational routes of exposure and endpoints associated with these routes are most appropriate to use in an RA.
2. In the revised CRA, a CEL (Comparative Effects Level) approach was used.
   a. The reason that a different approach was used from the oral exposure is that the ChE inhibition database for dermal and inhalational routes was more limited than for oral routes
   b. “Comparative effect levels (CELS) have been used to compare the relative potency of the OPs. CELS are dose levels from a given study with a defined range of effects. The CEL was defined as the dose causing a maximum of 15% brain cholinesterase inhibition.”
   c. The dose was not modeled but rather an observed response (i.e., experimental dose) in the female rat brain.
      1. Thus, the CEL is based on a similar toxicological response.

E. The index chemical for calculating RPFs remained methamidophos in the revised CRA.
1. Methamidophos met the two criteria of having a high quality database depicting inhibition of plasma, RBC, and brain ChE and it acted toxicologically through the common mechanism of action (i.e., inhibition of AChE).
2. The point of departure (POD) for methamidophos was 10% ChE inhibition (the dose causing this POD is called the benchmark dose 10 or BMD_{10}).
   a. “A POD is a point estimate on the index chemical’s dose-response curve that is used to extrapolate risk to the exposure levels anticipated in the human population.”
   b. This POD was used for oral, dermal, and inhalational exposures to the index chemical.
   c. The BMD_{10} is about the limit of sensitivity for detecting statistically significant ChE inhibition compared to the control.

F. Relative Potency Factor Determinations
1. The BMD_{10}s were first calculated for the oral exposure ChE depression data (Table 12).
   a. BMD_{10}s ranged over 5 orders of magnitude (Figure 11)
   b. Females were from 2-7 times more sensitive than males
   c. Selected BMD_{10} for frequently used OP insecticides
   d. Formula for calculating RPF for oral exposure (Distribution of RPFs shown in Figure 12)
      1. Oral RPF OPx = BMD_{10} index/BMD_{10} OPx
2. The CELs for dermal and inhalational exposures were represented by experimental doses causing similar levels of ChE inhibition
a. These levels of inhibition ranged from 0-15% ChE depression in the brain compared to the non-dosed control females
b. Formula for calculating RPFs for dermal and inhalational exposure
   1. Dermal & Inhalational RPF OPx = CEL index/CEL OPx

Table 12. BMD10s and RPFs for Oral Exposure to OP Insecticides Based on the Exponential Dose-Response Model for Female Brain Acetylcholinesterase Inhibition

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Female BMD10</th>
<th>Female RPF</th>
<th>Male BMD10</th>
<th>Male RPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>acephate</td>
<td>0.99</td>
<td>0.081</td>
<td>0.77</td>
<td>0.091</td>
</tr>
<tr>
<td>azinphos-methyl</td>
<td>0.86</td>
<td>0.093</td>
<td>1.14</td>
<td>0.061</td>
</tr>
<tr>
<td>bensulide</td>
<td>31.91</td>
<td>0.003</td>
<td>40.88</td>
<td>0.002</td>
</tr>
<tr>
<td>chlorethoxyfos</td>
<td>0.65</td>
<td>0.123</td>
<td>0.69</td>
<td>0.101</td>
</tr>
<tr>
<td>chlorpyrifos</td>
<td>1.48</td>
<td>0.054</td>
<td>1.5</td>
<td>0.047</td>
</tr>
<tr>
<td>chlorpyrifos-methyl</td>
<td>16.2</td>
<td>0.005</td>
<td>14.26</td>
<td>0.005</td>
</tr>
<tr>
<td>diazinon</td>
<td>6.24</td>
<td>0.013</td>
<td>9.62</td>
<td>0.007</td>
</tr>
<tr>
<td>dichlorvos</td>
<td>2.35</td>
<td>0.034</td>
<td>1.71</td>
<td>0.041</td>
</tr>
<tr>
<td>dicrotophos</td>
<td>0.04</td>
<td>2.000</td>
<td>0.04</td>
<td>1.750</td>
</tr>
<tr>
<td>dimethoate</td>
<td>0.25</td>
<td>0.320</td>
<td>0.35</td>
<td>0.200</td>
</tr>
<tr>
<td>disulfoton</td>
<td>0.07</td>
<td>1.143</td>
<td>0.1</td>
<td>0.700</td>
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<tr>
<td>ethoprop</td>
<td>1.37</td>
<td>0.058</td>
<td>1.35</td>
<td>0.052</td>
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<tr>
<td>fenamiphos</td>
<td>1.96</td>
<td>0.041</td>
<td>1.73</td>
<td>0.040</td>
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<tr>
<td>fenthion</td>
<td>0.24</td>
<td>0.333</td>
<td>0.18</td>
<td>0.389</td>
</tr>
<tr>
<td>fosthiazate</td>
<td>1.28</td>
<td>0.063</td>
<td>1.48</td>
<td>0.047</td>
</tr>
<tr>
<td>malathion</td>
<td>313.91</td>
<td>0.0003</td>
<td>212.02</td>
<td>0.0003</td>
</tr>
<tr>
<td>methamidophos</td>
<td><strong>0.08</strong></td>
<td><strong>1.000</strong></td>
<td><strong>0.07</strong></td>
<td><strong>1.000</strong></td>
</tr>
<tr>
<td>methidathion</td>
<td>0.25</td>
<td>0.320</td>
<td>0.24</td>
<td>0.292</td>
</tr>
<tr>
<td>methyl-parathion</td>
<td>0.67</td>
<td>0.119</td>
<td>0.7</td>
<td>0.100</td>
</tr>
<tr>
<td>mevinphos</td>
<td>0.11</td>
<td>0.727</td>
<td>0.15</td>
<td>0.467</td>
</tr>
<tr>
<td>naled</td>
<td>1</td>
<td>0.080</td>
<td>1</td>
<td>0.070</td>
</tr>
<tr>
<td>omethoate</td>
<td>0.09</td>
<td>0.889</td>
<td>0.14</td>
<td>0.500</td>
</tr>
<tr>
<td>oxydemeton-methyl</td>
<td>0.09</td>
<td>0.889</td>
<td>0.07</td>
<td>1.000</td>
</tr>
<tr>
<td>phorate</td>
<td>0.21</td>
<td>0.381</td>
<td>0.29</td>
<td>0.241</td>
</tr>
<tr>
<td>phosalone</td>
<td>6.93</td>
<td>0.012</td>
<td>7.88</td>
<td>0.009</td>
</tr>
<tr>
<td>phosmet</td>
<td>3.56</td>
<td>0.022</td>
<td>4.15</td>
<td>0.017</td>
</tr>
<tr>
<td>phostebupirim</td>
<td>0.37</td>
<td>0.216</td>
<td>0.4</td>
<td>0.175</td>
</tr>
<tr>
<td>pirimiphos-methyl</td>
<td>2.25</td>
<td>0.036</td>
<td>1.58</td>
<td>0.044</td>
</tr>
<tr>
<td>profenofos</td>
<td>20.58</td>
<td>0.004</td>
<td>24.98</td>
<td>0.003</td>
</tr>
<tr>
<td>terbufos</td>
<td>0.1</td>
<td>0.800</td>
<td>0.18</td>
<td>0.389</td>
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<tr>
<td>tetrachlorvinphos</td>
<td>60.69</td>
<td>0.001</td>
<td>369.27</td>
<td>0.000</td>
</tr>
<tr>
<td>tribufos</td>
<td>4.27</td>
<td>0.019</td>
<td>4.52</td>
<td>0.015</td>
</tr>
<tr>
<td>trichlorfon</td>
<td>31.74</td>
<td>0.003</td>
<td>58.49</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Figure 11. BMD10s estimated from the exponential model for the dose-response relationship describing female brain acetylcholinesterase inhibition

Figure 12. RPFs (Relative Potency Factors) for OP insecticides.

XI. Cumulative Exposure Assessment

A. Exposure assessment is based on pesticide residues found in food, water, and around residences (lawn, garden, and home)
   1. The exposure sources are food (dietary), drinking water, and residential.
   2. The pathways of exposure are oral (food and drinking water) and dermal/inhalational (residential)
a. One exception is that infants/children have an oral exposure route for residential exposure because of hand-to-mouth contact behavior.

B. Regional perspective on exposure from drinking water and residential use
   1. EPA has divided the U.S. in seven regions (Figure 13).
   2. The regions are based on major crop growing areas and their influence on surface and ground water.
   3. The regions also consider the unique climate patterns, pest patterns and potential socioeconomic patterns that influence residential pesticide use and expected exposure.

   ![Diagram of the seven regions of the U.S. used for conducting drinking water exposure assessment.](image.jpg)

   Figure 13. The seven regions of the U.S. that EPA used to assess regional differences in drinking water and residential exposure. Note that the regions are coded by letter (A-G). The numbers next to the letter codes represent the USDA 12 farming regions, which was used by EPA in the first draft cumulative risk assessment.

C. Dietary Exposure Assessment
   1. Derivation of residue data
      a. EPA uses actual monitored residue data for various foods
      b. USDA Pesticide Data Program (PDP) database
      c. FDA Surveillance monitoring program database
      d. FDA Total Diet Study (used to inform EPA of the validity of its estimations)
   2. Derivation of consumption data
      a. EPA uses the USDA database for foods consumption—CSFII (Continuing Survey of Food Intake)
   3. Exposure is determined by normalizing all of the residues in each of the foods to methamidophos equivalent exposures.
      a. The calculation is
      b. Methamidophos Equivalents = OPx residue (ppm) in food x RPF OPx
      c. The normalized residues are then multiplied by the mass of food consumed to obtain mass of pesticide residue as methamidophos equivalents.
      d. The pesticide mass consumed is then divided by the body weight to calculate exposure as mg pesticide/kilogram body weight/day.
D. Drinking Water
1. In each of the seven EPA defined regions, maps of OP use were overlain with maps of runoff and leaching vulnerability.
2. On top of these overlays, EPA considered the location of surface and ground water intakes for drinking water.
3. EPA chose the most vulnerable site (based on a combination of OP use, vulnerability, and location of intakes).
   a. For example, in the Northwest Region (B), EPA chose the Willamette Valley as a representative watershed for the whole PNW.
   b. EPA does modify the analyses by incorporating a factor for percentage of crop treated.
4. EPA used the models PRZM (Pesticide Root Zone Model) and EXAMS (Exposure Analysis Modeling System) to estimate residues in the water.
5. The residues were adjusted by the RPFs to get methamidophos equivalent residues.
6. Consumption of drinking water is assumed to be 2 L per day for adults (1.5 L for infants/children).
7. Multiplication of residues by volume gives mass of pesticide. Mass is then divided by an appropriate body weight to yield mg/kg/day of exposure from drinking water.

E. Residential
1. EPA used a calendar based model (Calendex™) to address the temporal aspects of the residential use of pesticides in 7 geographic regions throughout the United States.
2. Calendex™ delineates the critical timing aspects of seasonal uses of OP insecticides that result in exposure.
   a. Calendex also enables the identification of potential co-occurrences from multiple sources.
      1. For example, co-occurrences might include the exposure from home lawn and garden treatments, pesticides used on golf courses and applications made by governmental entities for the control of public health pests such as wide area mosquito sprays.
3. The specific residential exposures considered (owing to their potential for significant exposure and their recognized “critical” uses include,
   a. Golf course and lawn care applications
   b. Home gardens
   c. Wide area Public Health sprays
   d. Pet Treatments (includes aerosol, liquid, and powder uses)
   e. Impregnated pest strips (limited to closets and cupboards)
4. Only 10 OP insecticides had residential type uses at the time of the revised CRA (acephate, bensulide [actually a herbicide], dichlorvos, disulfoton, fenamiphos, fenthion, malathion, naled, tetrachlorvinphos, trichlorfon)
5. Much of the data for residential exposure comes from industry studies submitted to EPA.
   a. Unit exposure factors have been calculated per pound of pesticidal active ingredient applied for different application scenarios.
   b. Assumptions have to be made about the activities and associated exposure parameters (e.g., length of time, volume of air inhaled, dermal transfer).
XII. **Assessment of the Need for the FQPA Safety Factor**

A. Normally, EPA uses a 100-fold safety factor applied to the NOAEL
   1. The 100-fold factor represents interspecies (10X) and intraspecies (10X) extrapolation factors.

B. However, under the FQPA, EPA must use an extra safety factor up to 10X if infants/children are deemed more sensitive to a given pesticide than adults.
   1. EPA reviewed the literature on differential sensitivity of fetal, neonatal, and adult rodents to OP insecticides
   2. The agency indicated that the literature indicates that fetal and neonatal rodents have low levels of esterase activity (especially aliesterase or A-esterase, known also as oxonases), which would be important in detoxification
   3. At the same time, activity of microsomal P450 oxidase enzymes (specifically, CYP3A4) is higher in neonates, suggesting potentially higher rates OP activation to the oxon forms.
      a. CYP3A4 is also important in detoxification through a dearylation reaction.
      b. Rate of detoxification is slower than rate of oxidation (about 2.5 fold slower) as evidenced by the lower Km (~8.5 fold lower) for OPs involved in the latter reaction than the former reaction.

C. Based on its review of the submitted registrant data and the literature, EPA determined that only the OP insecticides dimethoate, omethoate (a metabolite of dimethoate), chlorpyrifos, and methamidophos could have a reduced FQPA safety factor of 1X.
   1. All other OP insecticides were assigned an extra FQPA safety factor of 3X

D. To apply the safety factor, EPA incorporated the 3X into the RPF.
   1. Thus, if an RPF was 0.10, then after application of the 3X factor, it became 0.30, making the potency even closer to the methamidophos index potency (thus all residues would be estimated as being three times higher)

XIII. **Cumulative Risk Characterization**

A. EPA uses a Margin of Exposure approach to characterize risk.

B. The MOE = NOAEL (mg/kg/d for AChE inhibition)/exposure (mg/kg/day)

C. Because methamidophos is the index chemical, and all residues and thus exposures are changed to equivalents of methamidophos, its NOAEL was used to calculate the MOE for the cumulative risk characterization (Table 13).

<table>
<thead>
<tr>
<th>Exposure Route</th>
<th>Sex</th>
<th>BMD10</th>
<th>BMDL</th>
<th>NOAELs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>F</td>
<td>0.08</td>
<td>0.07</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.07</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td>F</td>
<td>2.12</td>
<td>1.77</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>1.88</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>Inhalation</td>
<td>F</td>
<td>0.39</td>
<td>0.21</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.3</td>
<td>0.2</td>
<td>0.29</td>
</tr>
</tbody>
</table>

D. Normally, EPA will consider any MOE of 100 or greater to be acceptable.
E. To “capture” the entire distribution of the population, EPA calculates the MOE for various percentiles of the population’s exposure on each Julian date.
   1. The ideal percentile is the 99.9\textsuperscript{th}.
   2. Thus, if at the 99.9\textsuperscript{th} percentile of exposure, the MOE is 100 or greater, than we can interpret the significance as 99.9 percent of the population (i.e., 99.9% of all possible exposures) is exposed to a dose 100 times less than the dose not causing any significant cholinesterase inhibition (~10% inhibition or the magnitude of resolution of the cholinesterase test).

F. The three dimensional graph shown in Figure 14 indicates that the total MOE for all of the population at the 99.9\textsuperscript{th} percentile of exposures is less than 100 on all days of exposure.
   1. However, MOEs at the 99\textsuperscript{th} percentile or less exposures are closer to 100 or exceed 100.
   2. The exceedance of 100 at the 99.9\textsuperscript{th} percentile represents an extreme exposure potential that EPA implies is more artifact than reality.

G. The MOE approach by different exposure pathways allows an examination of the proportional contributions to exposure at the 99.9\textsuperscript{th} percentile.
   1. For example, food exposure to children 1-2 years old is probably pushing the MOE under 100 as shown for each exposure day in Figure 15.
      a. Note that total MOE represents the cumulative exposure for food, drinking water, and residential exposure.
      b. The foods contributing the greatest exposure by percentage were grapes (33%), pears (26%), apples with peel (13%), apple juice (10%), tomatoes (5%), raisins (4%), snap beans (3%), bell peppers (3%), potatoes without peel, cooked (2%), spinach (1%), cucumber (1%). All other foods contributed less than 1% of the cumulative OP exposure.
   2. Similarly, the residential exposures to children 1-2 years old (represented by the inhalational and dermal exposure MOE lines), are also contributing to the MOE less than 100 at the 99.9\textsuperscript{th} percentile of exposure. However, only the inhalational exposure pathway is contributing significantly to exposure (note that its line is less than 100; the dermal MOE line is greater than 100)
   3. When a 7-day moving average of exposure is calculated, the MOEs for 1-2 year olds at the 99.9\textsuperscript{th} percentile of exposure to food meet the MOE of 100 standard (Figure 16).
      a. But the residential exposures hover around an MOE of 70.
   4. Pertinently, drinking water exposure contributes very little to the total MOE level, indicating OP insecticide exposure from water sources are extremely low.
   5. Total MOE and individual source MOEs for adults all meet the standard of equaling or exceeding 100 at the 99.9\textsuperscript{th} percentile of exposure (Figure 17).
Figure 14. Total MOE for the U.S. population at all percentiles of exposure.

Figure 15. MOEs for children 1-2 years old at the 99.9th percentile of exposure.
Figure 16. MOEs for children 1-2 years old at the 99.9\textsuperscript{th} percentile of exposure calculated using a 7-day moving average.

Figure 17. MOEs for adults at the 99.9\textsuperscript{th} percentile of exposure calculated using a single days exposure.