Letter Health Consultation

ST. REGIS PAPER COMPANY SITE
CASS LAKE, CASS COUNTY, MINNESOTA

EPA FACILITY ID: MND057597940

APRIL 21, 2008

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333

Health Consultation: A Note of Explanation

An ATSDR health consultation is a verbal or written response from ATSDR to a specific request for information about health risks related to a specific site, a chemical release, or the presence of hazardous material. In order to prevent or mitigate exposures, a consultation may lead to specific actions, such as restricting use of or replacing water supplies; intensifying environmental sampling; restricting site access; or removing the contaminated material.

In addition, consultations may recommend additional public health actions, such as conducting health surveillance activities to evaluate exposure or trends in adverse health outcomes; conducting biological indicators of exposure studies to assess exposure; and providing health education for health care providers and community members. This concludes the health consultation process for this site, unless additional information is obtained by ATSDR which, in the Agency's opinion, indicates a need to revise or append the conclusions previously issued.

You May Contact ATSDR TOLL FREE at
1-800-CDC-INFO
or
Visit our Home Page at: http://www.atsdr.cdc.gov

LETTER HEALTH CONSULTATION

ST. REGIS PAPER COMPANY SITE
CASS LAKE, CASS COUNTY, MINNESOTA

EPA FACILITY ID: MND057597940

Prepared By:

Minnesota Department of Health
Under Cooperative Agreement with the
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

Protecting, maintaining and improving the health of all Minnesotans

December 14, 2007

Mr. Timothy Drexler
Remedial Project Manager
Superfund Division
U. S. Environmental Protection Agency (EPA)
Region 5
77 West Jackson Boulevard (SR-51)
Chicago, IL 60604

Dear Mr. Drexler:

The Minnesota Department of Health (MDH) is submitting provisional comments on the *second Draft Human Health Risk Assessment for the St. Regis Paper Company Site, Cass Lake, MN (HHRA)* received from the International Paper Company (IP) on September 28, 2007. This second draft of the *HHRA* is far longer and complex than the first (2005) draft (already long and complex). The additional material has little relevance as a response to EPA's specific required changes to the 2005 draft HHRA, and contains much added material of little or no use. MDH did not review most of the calculations done by IP; but it cannot be assumed that these were done correctly (as documented below). We may have additional comments on this as well as other matters when we receive and have had a chance to review comments from the Leech Lake Band of Ojibwe (LLBO), the Minnesota Pollution Control Agency (MPCA) and the EPA. We are especially interested in comments prepared by Eric Morton of TetraTech for EPA. These comments were presented in a telephone conference call on November 19.

Our findings, spelled out in more detail in the review below, are that:

- The conclusions of the 2007 draft HHRA are not usable for decision-making;
- The risk assessment process has already been far too long; requiring IP to write another draft is self-defeating because the third document is likely to be even longer and more ungainly than the second document and past experience suggests it will take another two years;
- EPA may (or may not) be able to use *selected* cancer and non-cancer risk calculations from the current document for all exposure media analyzed *including fish* as a starting point for its own calculations;
- EPA should include additional risks where appropriate (e.g., risk from surface deposition onto garden crops, eating of fish eggs, exposures to shallow groundwater, etc.);

- EPA should appropriately consider uncertainties which suggest that the current draft is biased and that risks are likely to be underestimated;
- EPA should use the risk calculations in conjunction with uncertainties and generate a set of *conservative* remediation goals for soil and sediment;
- EPA should ignore IP's specific risk calculations tied to specific exposure point concentrations and should instead use its own set of validated environmental sampling data to:
  1) determine where more environmental sampling is needed in order to ensure that the site is appropriately investigated in light of the remediation goals, and then carry out the needed environmental sampling;
  2) ensure that the site is cleaned up consistent with remediation goals; and finally,
- Additional environmental sampling and subsequent remediation should be done within a short time frame.

Specific Comments follow:

Chapter 1, Introduction:

Page 1-2. The conclusion that there are no site-related adverse risks for non-cancer effects is obviously wrong (see below). The conclusion that the HHRA identified no site-related cancer risks that exceed EPA's acceptable risk range is also wrong (see below).

Page 1-2, page 1-14. It is implied that exposure scenarios evaluated in the HHRA for both cancer and non-cancer effects include interim remedial actions to reduce exposures to yard soil and house dust. But on page 1-14 the (presumably correct) assumption is made that housecleaning and dust suppression applications will not continue once a permanent remedy is selected. IP can't have it both ways. In fact, it is inappropriate to include interim remedial actions in any risk scenario, including current or future scenarios. Modifying risk scenarios, especially exposure point concentrations, to take into account temporary interim measures is inappropriate. Only the so-called "past" scenario is valid for decision-making (but this is not even mentioned in the summary statements).

Page 1-4. There is no mention that the site is located within the boundaries of a reservation.

Page 1-12. Excavation and placement of contaminated material in containment vault: It should be mentioned that large areas of the site were graded and soil was moved throughout the site without proper site characterizations, resulting in dioxins and other site contaminants being scattered across the site and deposited in high concentrations in "remediated" areas. The use of uncharacterized fill material is problematic and has lead to cross-contamination. The cross-contamination issues have been raised numerous times by MDH.

Page 1-15. The list of references used to conduct the HHRA should include the MPCA PAH guidance for soil and air (http://www.pca.state.mn.us/air/aera-ci.html , and http://www.pca.state.mn.us/publications/risk-tier2srv.xls). The list should also include MDH groundwater rule (http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/rules.html, and MN. Stat. Sec. 103H.201 - 103H.280) and MDH Health Risk Values for Air (http://www.health.state.mn.us/divs/eh/risk/guidance/index.html). MDH has requested numerous times that all soil, groundwater and sediment samples be analyzed for the full set of carcinogenic PAH compounds found in the references listed above. It is troubling that site operations utilized PAHs extensively, yet most of the samples were not analyzed for the full list of carcinogenic PAHs needed to fully characterize human health risks.

Chapter 2, Data Evaluation and Selection

As with the first draft of the HHRA, the main problem with this risk assessment relates back to the highly biased selection of data for evaluation.

A general comment concerns data use and selection criteria. There is a lack of transparency in descriptions of sample validation, sample selection, statistical evaluation and other steps in the EPC derivation. The reader is not able to follow each step and duplicate the risk calculations in Chapter 4.

A general comment concerns the process for selecting COPC's. The process for selecting COPCs to be retained is biased to prevent a true assessment of cumulative exposures. If a given chemical is detected in multiple media, but does not exceed the screening criteria in any of those media it is completely ignored, even though the cumulative exposure may be significant. Similarly, if a given chemical is detected above the screening criteria in one medium, and is present but below the screening criteria in others, it is dropped from consideration in those media, again masking the true level of exposures. If a chemical is detected above the screening criteria in one medium, it should be included in the EPC calculations using the concentrations in all of the media where it has been detected. Similarly, if a chemical is detected in multiple media, but does not exceed the screening criterion for any, then a "hazard index" calculation should be performed by dividing the maximum concentration detected in a given medium by the screening criteria for that medium and summing the values; if the sum is 1 or greater, the chemical should be included in the EPC calculations using the concentrations in all of the media where it has been detected. The only exception would be if the maximum concentration is within the range of natural background concentrations detected in the reference areas, in which case the contribution from that medium should not be included in the EPC calculations.

Fish data selection and risk assessment

These comments assume in general that the data and statistics are correct except where noted, and rely on EPA's evaluation of the completeness of the data and appropriate

statistical treatment. The main focus was on dioxins in walleye and whitefish fillet and the overall approach related to fish fillets.

Our overall conclusion is that **risks from fish consumption should be included in the total risk calculation.** This conclusion is in agreement with comments of Eric Morton of Tetratech in the telephone conference call of November 19, 2007.

Statistical analysis shows dioxins concentrations in walleye and tulibee/whitefish fillets from the site are higher than reference sites. Higher concentrations in these species, in particular, are of concern because they are the ones most consumed by tribal members. Needing "confirmation" of differences is not appropriate for public health risk assessment.

Differences in dioxin concentrations in fish between reference and site waters are underestimated due to decisions about data use and data exclusions, including:

- Low frequency of detection for dioxin/furan congeners, e.g. page C-14 perch-fillet data discussion. Site data had a 40% detection frequency and reference data (LLBO Pilot Project) had only a 7% detection frequency.
- Small sample sizes.
- Exclusion of eggs and partials from exposure considerations. Page C-3 states partials are not relevant for human health risk assessment. What evidence do they have to support that statement? They say eggs were excluded due to small sample size. IP was directed to use maximum detected values for small sample sizes (see Data Issues Section of Change Items List from Tim Drexler). Also this is inconsistent: other data sets with small sample sizes were included and evaluated. Eggs were part of the agreed upon work plan and should therefore be included. Eggs would not necessarily replace some fish meals, as implied (4-26); they could be in addition to fish meals.
- Lack of reference data for whitefish; use of tulibee for reference comparisons.
- EPC for fish is calculated by combining all fish species data (p. 4-35, 4-37). The report states that this is appropriate because no difference was seen between fish species. Differences were examined between site and reference fish by species. No evaluation of between species differences was reported. In addition it is well known that contaminant concentrations are dependent on fish species. Data in C-1 indicates there are differences in TEQs between species in site and reference data.
- Split sample decision rules in general - averaging of split samples.
- Using SQL versus DL? If DLs are more similar between labs than SQLs, how does use of ½ SQL rather than ½ DL to censor non-detects for dioxins impact assessment of differences between reference and site fish?

- Excluding samples where detection limit exceeded highest detected value.
- Analysis of congener profiles may reveal further differences between site versus reference fish. Due to the timeframe for this review this analysis was not carried out.
- Excluding reference lakes from the NLFTS due to trophic status. There are additional walleye data from lakes that could logically be included as reference. Including these four lakes reduces the mean TEQ concentration for walleye from the NLFTS. The total TEQs (ND=0) for all four excluded lakes were lower than the any of the included lakes. Cass Lake had the highest total TEQ (ND=0). The TEQ DF (ND=0) from Cass Lake is an order of magnitude higher than walleye from the other NLFTS sites.

NE Minnesota Walleye Data from NLFTS

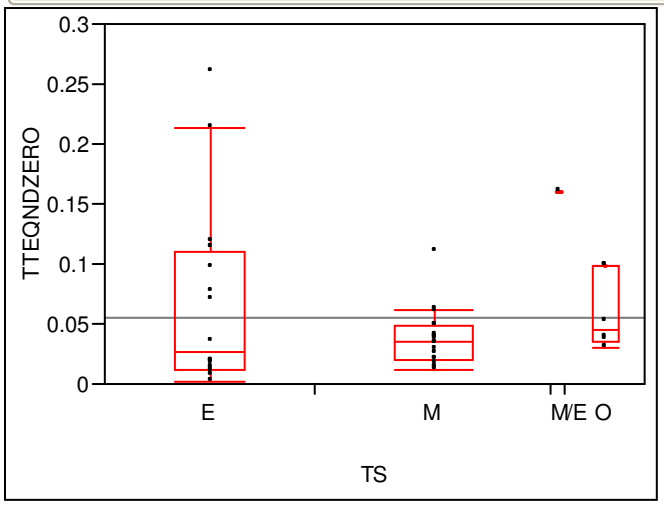
NLFTS SampleID	Site_Name	Total TEQ ND=0	TEQ DF ND=0
MN020980PS	Red Lake	0.006293	0
MN000460PS	South Mcdougal Lake	0.011022	0
MN021110PS	Vermilion Lake	0.015917	0.003
MN011010PS	White Iron Lake	0.018162	0
MN990081PS	Fox Lake	0.018526	0
MN000180PD	Woman Lake	0.038292	0.02
MN030933PS	Mille Lacs	0.040019	0
MN000180PS	Woman Lake	0.048318	0.003
MN030235PS	Snowbank Lake	0.058761	0
MN990205PS	Cass Lake	0.098134	0.037

* first four lakes were not included as reference sites in risk assessment

Selection of Reference Lakes from the NLFTS

MDH comments from January 30, 2006 on the selection of reference lakes were not addressed. It is still not clear if NLFTS data for Cass Lake walleye were included in the risk assessment; this data is not listed in Table C-1. In general, the basis for the selection criteria is not adequate. Excluding a lake based on trophic status is not justified. In fact dioxin TEQ data from the NLFTS do not show a relationship between dioxin TEQ and trophic status.

Oneway Analysis of TTEQNDZERO By TS Composite_Type=Predator



Missing Rows 18

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
E	0.002256	0.005082	0.011597	0.026577	0.109517	0.227632	0.259712
M	0.012319	0.013019	0.020347	0.035656	0.048477	0.066497	0.110766
M/E	0.160664	0.160664	0.160664	0.160664	0.160664	0.160664	0.160664
O	0.029976	0.029976	0.035363	0.044649	0.098271	0.098682	0.098682

Inconsistencies noted in HHRA Report:

Table 2-7
All data sets considered in this analysis are presented in Tables 2-1 through 2-7 (fish is 2-7) (page 2-3 section 2.2 last sentence). EPA NLFTS samples are not listed in Table 2-7. Egg samples are listed in Table 2-7 and some of these have Dioxins/Furans marked with an "X" indicating to include in risk assessment.

Tables 2-18 and 2-19
Table 2-19 lists reference samples to exclude but doesn't appear to be consistent with Table 2-7. For example for Sample Event 2002 LLB2, Table 2-7 has an "X" under Dioxins/Furans for samples 02LLW009 and 02LLW010 while Table 2-19 lists these same samples as excluded.

Table C-11. Results from Wilcoxon Comparison for Site vs. Reference.
Project specific reference walleye n=3 so how can table C-11 say "site is not greater"? According to text on C-9 statistical tests were performed only when both data sets contained at least five values.

Soil Data Selection and Risk Assessment

Considering the site was a wood treatment facility that used PAHs extensively, why were very few soil samples and other media analyzed for the full list of carcinogenic PAHs? Why have so few soil samples been collected deeper than 12 inches on such a large site? These comments have been made numerous times dating back to the EPA investigation in 2001. Additionally, the MPCA's Risk Based Evaluation Guidance Manual defines the first 4 feet as accessible, and the 4-12 feet (below ground surface) as potentially accessible soil.

IP excluded soil data from consideration for reasons having nothing to do with "rules" described in Chapter 2. Table 2-1 gives numerous examples with comments such as the following:

"Excluded: Excavated in 2004 removal action." What are the soil concentrations at the base of the excavations? The removal action removed soil to a depth of 12 inches or less in most areas. These data should be included in the risk calculations.

"Sample of stained material in roadway collected at unknown depth." These data should be used, and it should be assumed that they were surface samples.

"Excluded: Topsoil used to backfill excavated areas on the Allen property during the removal." These data should be included. Many excavations were to a depth of as little as 4 inches.

"Split selected: Positive bias in split sample results." EPA should verify that the results with the higher value should be selected.

"Covered by a geotextile fabric and a minimum of 4-inches of gravel per the work plan…" This is an inadequate excavation depth. The sample should be included.

"Excluded: property burned down." This is not a reason to exclude a sample.

Sediment Data Selection and Risk Assessment

The manner in which reference area samples are compared to samples at/near the site is not valid and is used to disqualify data that should be included in the EPCs. Barr/IP apparently compared the entire "site area" data set to the entire "reference area" data set. But the "site area" data set contains results from areas both near and far removed from the source areas, creating a much larger range of sample results that includes background levels. Comparison of reference data to particular site areas, especially those closer to sources, is far more revealing. For example, when the reference area arsenic sediment data set (ND – 13.1 mg/kg) is compared to the overall site area sediment data set (ND – 29 mg/kg), there is no "statistical" difference between them. But when the reference area

data set is compared to the sediment data from Fox Creek near the city dump (9 – 29 mg/kg), the difference is obvious. Clearly, the sediment in Fox Creek near the city dump has higher arsenic levels than the background levels in the reference area.

Table D1-11.
No sediment samples have been analyzed using the extended PAH list – doesn't this have to occur to determine if these compounds need to be included in the COPC?

Groundwater Data Selection and Risk Assessment

In 1998, the list of PAHs for which groundwater samples were analyzed was significantly shortened. As noted in the MDH draft *Public Health Assessment for Groundwater, Surface Water and Sediments (December 2005),* the PAHs dropped from the analyte list accounted for a significant percentage (24-90%) of the nPAH and Total PAH in 24 monitoring wells. While most of these compounds did not exceed human health criteria, two did: carbazole (wells 118, 402, 405, 409, 2401, and 2403) and dibenzofuran (wells 118, 207, 401, 402, 405, 409, 2401, and 2403). These compounds should be retained as COPCs and included in the EPC calculations using the concentrations in any media where they were detected.

Furthermore, groundwater PAH concentrations should be compared to the MDH Total Petroleum Hydrocarbon Health Based Value.

Surface Water Data Selection and Risk Assessment

Table D1-12.
PCP was excluded from the COPC list, even though it was detected in 40% of the samples. PCP is one of the primary COPCs for the site, and exposure to it occurs through multiple pathways; it should be retained as a COPC and included in EPC calculations in order to evaluate cumulative exposures.

Chapter 3, Chemical Sources, Release Mechanisms, and Transport Pathways

3.1.2.3, p. 3-8. Second and third paragraphs reference dumping of sludge in the southwest area, but Figure 1-2 does not show any dumping locations mentioned in the text.

Chapter 4, Human Health Risk Assessment

General Comments

- The HHRA should not include the interim remedial action (4 inch soil cover) as a dilution factor. On October 28, 2003 Patricia Bloomgren, Director of the

Division of Environmental Health, wrote to William Muno, Director of the EPA Superfund Division: "The removal action should be taken so that it complements, rather than interferes with, any future remedial actions performed as a result of human health and ecological risk assessments." The letter went on to state: "Soil removal at this depth [4 inches] will not protect gardeners, children digging, people playing sports, or doing any number of ordinary activities. It will not prevent wind erosion from uncovering more contaminated soil." On June 23, 2005, Rita Messing, Supervisor of Site Assessment and Consultation and Daniel Peña, Health Assessor in the same unit, wrote to Tim Drexler, Remedial Project Manager: "…MDH believes that it is important to carry out the interim plan in such a way that the ultimate remedial action is not compromised. The interim plan calls for covering and seeding residential yards. MDH recommends that soil levels used to evaluate remedial actions not include the dilution caused by the interim action…." The properties included in the IRA should not be referred to as remediated in the text.

- It is unacceptable for the residential exposure scenarios to exclude fish consumption.
- It is prudent and reasonable to consider the construction worker and utility worker to be a resident. A site resident is currently a public works employee of Cass Lake. Additionally, in a small town, the construction worker and the utility worker are likely the same person – in Cass Lake they may also be a tribal member.
- The St. Regis Superfund site HHRA should use the same garden exposure factors used in EPA's HHRA for the South Minneapolis Neighborhood Soil Contamination Superfund site. Treating the two populations differently in terms of garden vegetable consumption is not justifiable.

Conceptual Site Model

4.1.1, p. 4-1. The entire site area is a reservation. This was omitted from the description.

4.1.3, p. 4-4. The section does not adequately discuss or present any reasonable institutional controls as required by MN Uniform Environmental Covenants Act, Minn. Stat. Ch. 114E (Supp. 2007), and other MN rules and regulations. Any institutional controls will have to be coordinated with both the City of Cass Lake and the Leech Lake Band of Ojibwe. Until that time, the future land use assumptions for the entire site remain questionable at this time. In fact, the City of Cass Lake zoning ordinance permits public parks and playgrounds, as well as any number of commercial uses in the area described as being reserved for industrial use.

4.1.3.1, p. 4-5. The assumption that subsurface soils are generally lower in concentrations than surface concentrations is highly uncertain due to cross-contamination issues and very limited number of soil samples collected deeper than 12 inches. Based on the summary review of the soil date evaluated for use in the HHRA, it appears that **only three soil samples deeper than 12 inches** were evaluated in the HHRA (see table 2-1). Furthermore, it appears that only one (J29-29 (12 -24)) of the three samples was analyzed for PAHs, and all were located in the treatment facility operable unit. The lack of soil data deeper than 12 inches below grade has been raised by MDH numerous times dating back to the EPA site investigation in 2001.

The current and future residential exposure scenario must include ingestion of both surface and root crops (see general comments). Dioxin root uptake by garden plants is not the only pathway through which residents can be exposed. Surficial deposition of dioxin contaminated dust on the exterior of edible garden greens and plants in the tribal lifeways and residential scenarios must be included in risk calculations.

4.1.3.1, p. 4-6. The residential exposure scenario does not include dermal contact with contaminated groundwater. Groundwater is very shallow over much of the eastern portion of the site, even expressing itself as surface water in some of the wooded areas. We know that children have dug holes as deep as two feet in some portions of Area A, which could allow them to come into contact with the groundwater. Dermal contact with groundwater should be part of the residential exposure scenario, at least for children, if not adults.

4.1.3.4, p. 4-7. Under the recreational scenario the report says people "might" be using non-residential properties in Area A for recreation. There is so much obvious evidence of this usage, that the report should not qualify this and instead say that people "are" using those areas.

4.1.3.3, p. 4-7. It is reasonable to assume that the current and future worker/utility worker receptor could also be a site resident and or a tribal member. A current site resident is also a public works employee for the City of Cass Lake.

4.1.4, p. 4-8, and 4.1.4.2, p. 4-10. It is reasonable to assume that the current and future worker/utility worker receptor could also be a site resident and/or a tribal member. Currently, a site resident is also a City of Cass Lake public works employee.

4.1.4.1, p. 4-9. Was contaminated dust inclusion in honey considered in the subsistence/tribal lifeways exposure scenario?

Identification of Chemicals of Potential Concern

4.2.3.1, p. 4-13. The last paragraph incorrectly lists the MPCA Residential Soil Reference Value for Dioxin as 200 ppt. The referenced St. Regis Soil Health Consultation lists the dioxin SRV as 20 ppt in Appendix F (see

http://www.health.state.mn.us/divs/eh/hazardous/sites/cass/stregis/soilshcapendf_h.pdf). The current dioxin **SRVs are 20 ppt and 35 ppt for residential and industrial settings, respectively** (see http://www.pca.state.mn.us/publications/risk-tier2srv.xls). Please list the correct MPCA Dioxin SRVs throughout the HHRA.

4.2.3.2, p. 4-14. Barr has created their own sediment screening criteria, based on soil PRGs and adjusted for lower exposure frequency, that are orders of magnitude larger than the values developed by MDH for the U.S. Steel site and other PAH sites. They assume shorter skin contact than with dry soil, when in fact sediment is likely to adhere longer than dry soil because it is wet. They apparently do not include any factor for incidental ingestion or inhalation as part of their "screening criteria", even though these pathways will be completed for several of the exposure scenarios where sediments are encountered (recreational, subsistence or traditional tribal life-ways).

4.2.4.1, p. 4-16-17. The second paragraph does not note the residential area north of the tracks as exceeding the 50 ppt dioxin screening level. Additionally, the referenced Appendix Table D1-1 does not note the correct Region 9 EPA Residential Dioxin PRG. Table D1-1 through D1-6 do not list all the carcinogenic PAHs used by the MN to evaluate cancer health risks from exposure to wood treatment facilities. The tables do not clearly describe what carcinogenic PAHs were evaluated for each exposure scenario. The same can be said for Table 4-1. Without this critical information the reader is not able to evaluate if the cancer risk has been fully characterized.

See also comments above for Groundwater, Surface Water and Sediment Data Selection.

4.2.4.2 and Table D1-11. PCP was excluded from the COPC list, even though it was detected in 16% of the samples. PCP is one of the primary COPCs for the site, and exposure to it occurs through multiple pathways; it should be retained as a COPC and included in EPC calculations in order to evaluate cumulative exposures.

4.2.4.2, p. 4-18. As described above in the comment on selection of sediment data, the comparison to reference area sediment samples to site samples has been used inappropriately to disqualify arsenic from inclusion as a COPC.

Section 4.2.4.2, p. 4-18: The report incorrectly suggests that only samples from Fox Creek and the channel exceed their screening levels for dioxins/furans. Using the screening standards developed by MDH for use at the U.S. Steel site, the Fox Creek delta at Pike Bay, the wetlands adjacent to the channel, deep hole #1 in Pike Bay, and deep hole #1 in Cass Lake (EPA samples, 2001) all exceeded the screening levels by 3-5 orders of magnitude, and exceeded the reference area concentrations by 1-3 orders of magnitude. All of these areas need to be considered in the EPC calculations.

4.2.4.4, p. 4-19. The third paragraph seems to suggest that consideration of dioxins in groundwater for the utility worker scenario should be ignored because it was likely associated with NAPL in the wells where detected. If utility workers encounter areas of the site where NAPL is present, how will the associated levels be accounted for if not through the groundwater component of that scenario? And, as discussed above regarding Area A exposure scenarios, children have been known to dig deep holes while playing in non-residential portions of Area A. Exposure to dioxins via groundwater dermal contact should be included in the residential EPC calculations for children.

4.2.4.4, p. 4-19. The HHRA has not considered the use of MN's Health Based Value for total petroleum hydrocarbons (200 ug/l, pyrene surrogate) as a screening value. The tribal lifeways scenario should consider groundwater as a source of drinking water.

4.2.4.4, p. 4-19 - 4-20. The presence of NAPL in W2401, and detections of individual PAHs above their solubility limits, may be a reason for excluding the 2006 data from this well. However, it should not be used to further exclude all detections in that well of individual PAHs that also have been detected elsewhere in the groundwater (i.e. acenaphthene, fluoranthene, and pyrene), particularly as these compounds have similar target organs (acenaphthene and fluoranthene – GI Tract/liver; fluroanthene and pyrene – kidney) and detections even below the HRL or MCL could result in additive concentrations of concern.

Exposure Assessment

4.3.1.1, p. 4-23. As discussed above, children may have dermal contact with groundwater in the non-residential portions of Area A. This should be added to the residential scenario.

4.3.1.3, p. 4-24. It is reasonable for the onsite worker and utility worker to be the same person, and they may also be a site resident.

4.3.2.1, p. 4-26. Eggs would not necessarily replace some fish meals, as implied; they could be in addition to fish meals.

4.3.2.1, p. 4-29. It is not practical to use BaP comparison concentrations that cannot be verified as wet or dry weight.

4.3.3.1, p. 4-34**.** In general MDH agrees with the last sentence in the 3rd paragraph: "Concentrations from the individual or multiple residential properties were not aggregated to calculate an area-wide average because people are expected to have the majority of their soil contact on their own properties." This should also apply to the residential samples collected north of the railroad tracks. One of the composite sample results, composed of several residential properties, exceeds the ATSDR dioxin 50 ppt screening level, and the MPCA dioxin SRV. Therefore, MDH requests that individual

yards north of the tracks be sampled for dioxin, so each resident can be given yard specific exposure advice.

4.3.3.2, p. 4-36. The use of the interim remedial action (3-4 in) soil cover as a dilution factor is not acceptable (see general comments). The MPCA considers the first 4 ft soil accessible in a residential setting. It is not clear that the soil samples were analyzed for full list of carcinogenic PAHs. The Barr 2006 table 3 reference does not match the text discussion of soil TEQdf and BaPEs results. The Barr 2006 reference is a groundwater monitoring report. Second paragraph. The Allen property clearly exemplifies how dioxin concentrations can vary wildly due to cross contamination and soil alterations. Why is the Allen property, potentially the most dioxin contaminated residential property, still lacking BaPE results?

4.3.3.2, p. 4-35, 4-37. EPC for fish is calculated by combining all fish species data. The report states that this is appropriate because no difference was seen between fish species. Differences were examined between site and reference fish by species. No evaluation of between species differences was reported. In addition it is well known that contaminant concentrations are dependent on fish species. Data in C-1 indicates there are differences in TEQs between species in site and reference data.

4.3.3.2, p. 4-36 to 4-37. The averaging of the soil data from the Allen residence (as detailed in the footnote on p. 4-37) serves simply to further reduce the EPC. The results are already derived from averaged composite samples, and a second averaging is not acceptable. EPC's should not be "recalculated." Original, pre-IRM data should be used throughout.

Section 4.3.3.2, p. 4-37. Combining data from Fox Creek, the channel, and Pike Bay may be helpful from a statistical perspective, but is not helpful from a public health perspective. People may use all three areas, or they may use only one – if that one area is Fox Creek, they will have a greater exposure than if they "average" their use across the three areas. An EPC for use of all the areas, but in order to develop an RME, an EPC should also be calculated for the worst of these areas, and that would be Fox Creek near the city dump.

4.3.3.2, p. 4-39. In order to distinguish site from background, especially for evaluation of fish data, in order to remove "noise," TEQ's should be calculated using zero to characterize non-detected congeners. This comment has been made repeatedly over the past 5 years. See also comments above for fish data evaluation.

4.3.3.2, p. 4-39. Last paragraph. The lack of deeper soil samples is an unacceptable data gap dating from the EPA 2001 investigation and perpetuated with the IP investigation. It is important for a soil investigation to have sufficient data to characterize extent and magnitude of contaminants both vertically and horizontally in order to carefully define risks to human health.

4.3.3.2, p. 4-40. It is inappropriate for IP to state that "subsurface soil concentrations are typically lower than surface soil concentrations at the same location" when only three soil samples deeper than 12 inches were evaluated in the HHRA. More troubling still is IP's conclusion that "restricting the HHRA to surface soil concentrations likely results in conservative (protective) risk estimates." IP's conclusions based on the soil data are highly uncertain and do not take into account cross contamination issues. Table 4-2. Summary of Uncertainties states that "the exclusion of subsurface soil data has a low potential to overestimate risk." IP asserts that "surface soil concentrations tend to be higher than subsurface concentrations. Activities that mix surface and subsurface soil would tend to decrease concentrations remaining at the surface." This conclusion is not substantiated when subsurface soil data are virtually nonexistent. IP was asked to change this conclusion in the first draft.

4.3.3.3. p. 4-41. IP utilizes a vegetative cover value of 0.5. The MPCA SRV calculations use the following vegetative cover values:

- Residential scenario = 0.5
- Industrial scenario = 0.0
- Recreational scenario = 0.25

These values are specially suited for the St. Regis site where there are sandy soils, dirt roads, and most of the site is uncovered.

Section 4.3.3.3, p. 4-44. Is it reasonable to assume that utility trenches will be only 4 ft. deep simply because that is the depth to groundwater? Given the depth of frost in northern Minnesota, most utilities are buried 6 feet deep and presumably they could use pumping to allow excavation below the water table.

4.3.3.3, p. 4- 46 to 4-47. It is not acceptable that IP excluded the consumption of surface grown vegetables and greens. The ingestion of surface garden vegetables is part of RME residential exposure scenario. It is misleading to present the residential exposure scenario as including garden vegetable ingestion when it does not include surface grown crops.

4.3.4.1, p. 4-52. It is reasonable to assume that the utility worker (short-term exposure) and the construction worker (long-term exposure) might be the same person in a small town, and also a site resident.

4.3.4.2, p. 4-53. The exposure frequency of 83 days/yr is not protective enough for a resident. The HHRA should not use a recreational exposure duration to represent a residential scenario. A resident is likely to be outside in their yard most everyday of the year when the weather is reasonable. Residents spend more time in their yards than time spent away recreating.

4.3.5.1, p. 4-60. The referenced EPA document (Guidance Manual for the Integrated Exposure Uptake Bio-kinetic Model for Lead in Children, 1994) for partitioning dust and soil exposure states the following:

> ".. the option to allocate a portion of the ingested dust to dust derived from soil that is ingested during outdoor play activity … is important when there are differences between the bioavailability of dust derived from soil and dust in the home, when house dust is thought to be mostly of soil origin and each are expected to have similar biovailability, the designation of this fraction is a moot point. It is in cases where house dust differs significantly from soil derived dust that soil/dust ratio becomes important."

Indoor dust at the site is derived from out door soil. Additionally, smaller dust particle size and increased digestible organic content found in dust generally result in increased bioavailability. IP should therefore increase the bioavailability factor used in the house dust dose calculations. The partitioning between dust and soil is an unnecessary complication.

4.3.5.1, p. 4-63. The USEPA (2002h) reference defining a construction worker and outdoor worker does not take into consideration the likelihood that workers in small towns can be site residents who perform the tasks of both the construction and outdoor workers.

4.3.5.2, p. 4-64. IP appears to use a soil/dust dioxin relative bioavailability factor (RBA) of 0.5. The PCA uses a 0.55 RBA for dioxin in soil. It is also reasonable to utilize a larger RBA for dusts. Other RBA differences noted are as follows:

Contaminant	IP Relative Bioavailability	MPCA Relative Bioavailability
Napthalene	0.6	0.8
BAP	0.6	0.8
PCP	0.9	1.0

MDH recommends that using MPCA Soil Reference Value RBAs in the HHRA. Also note that text RBA values do not match the table 4-11 values.

Parameter Value Tables, Pp. 4-67, 4-76, 4-79, 4-90, 4-96, 4-99, and 4-101. Please list all parameter values for each scenario in the tables for clarity. Referring the reader to the text to find parameter values is burdensome and not helpful.

4.3.6.3, p. 4-72. The following table summarizes IP's soil adherence parameter values that differ from the MPCA SRV soil adherence factors (RME) :

Receptor	IP AF	MPCA AF

Residential Scenario RME		
Child (< 6 – 18 yrs)	0.2	0.2
Adult (>18-33 years)	0.07	0.13
Recreational Scenario RME		
Adult	0.07	0.35
Child (< 6 – 18 yrs)	0.2	0.35

4.3.6.3, p. 4-73. The suggestion that sediments underwater are "likely to be washed off the skin before the individual reaches shore" is contrary to the experience of anyone who has ever waded or swam in an area with silty or muddy sediments and returned to shore with silt and clay clinging to their legs and feet.

4.3.6.3, p. 4-74. Why is it "unlikely that loadings of Fox Creek and the channel area sediment on skin would reach the monolayer coverage required to attain the adherence factors found in the Shoaf et al. studies"?

4.3.11, p. 4-99. Why does IP's HHRA not include consumption of surface grown produce such as salad greens, tomatoes, and herbs? Region 5 EPA's HHRA for residents living on the South Minneapolis Superfund site includes the consumption of both root and surface grown vegetables. Cass Lake residents should not be treated differently than South Minneapolis residents in terms produce consumption rates, exposure frequency, and exposure duration parameters without justification.

Toxicicity Assessment

The toxicity assessment for dioxins is not in agreement with State of Minnesota policy. This policy appears at:

http://www.health.state.mn.us/divs/eh/risk/guidance/dioxinmemo2.html , and
http://www.health.state.mn.us/divs/eh/risk/guidance/dioxinmemo1.html).

These policies are also attached to this document.

IP also refers several times to the NAS/NRC report (2006). We are attaching slides from a talk given on September 17, 2007 by David Eaton, the chair of the NAS committee, at a conference at Michigan State University. These slides summarize salient points from the report. We are also attaching slides from a talk given by Michael De Vito, Chief, Pharmacokinetics Branch, EPA at the same conference. Conference proceedings are available at:

http://cit.msu.edu/Superfund/Dioxin%20Workshop.html

More specific comments follow.

4.4.2 and 4.4.2.1, p. 4-107-108. We agree with the statement that non-cancer endpoints may be a greater public health issue. However, ATSDR's chronic MRL (which is used in the HHRA, and is based on reproductive effects in the Rhesus monkey) may not be adequately conservative. It is simply the best evaluation that we have at the present time. DeVito (slides 20,21) indicates that other sensitive endpoints could be chosen, and that perhaps the immune system may be the most sensitive endpoint. Furthermore, human body burdens of dioxins are already at or near the ED01 for many of these non-cancer effects, so that the "margin of exposure" for non-cancer effects of dioxins is small and possibly even negative. These calculations are not based on the traditional RfD divided by uncertainty factor approach but are based on calculating equivalent body burdens for dioxins. This is the approach recommended by NAS (Eaton, slide 34).

4.4.2.2, p. 4-108-109. IP neglects to mention that just as the NAS/NRC did not endorse the EPA revised cancer slope factors (1E+6/(mg/kg-d) based on human data and 1.4 E+6/(mg/kg-d) based on animal data, neither did the NAS/NRC endorse the old slope factor of 1.5/(mg/kg-d). The point is that EPA *does not have a cancer risk assessment policy*. The State of Minnesota, however, does have such a policy. It is to use the slope factor based on animal data: 1.4E+6/(mg/kg-d). The reasons for this are spelled out in the attached policy document. MPCA has used this policy document to calculate Soil Reference Values for dioxins in soil of 20 ppt (residential) and 35 ppt (industrial). For present purposes, it is sufficient to note that this slope factor is neither the lowest nor the highest factor that could be derived (see for example Eaton's slides. Most importantly, it incorporates use of body burden as a dose metric: an approach endorsed by the NAS committee (cf. Eaton's slides). The old slope factor does not incorporate this more modern approach, and hence is not regarded as a valid decision-making tool in Minnesota.

Thus, as a minimum, MDH concludes that the higher of the two slope factors used in the HHRA should be chosen for decision-making: i.e., 1E+6/(mg/kg-d). The State of Minnesota may choose to re-calculate cancer risks using the preferred slope factor of 1.4E+6/(mg/kg-d) as we develop recommendations for further sampling and site remediation.

4.4.2.3, p. 4-110-111. From the standpoint of risk assessment it does not matter whether 2,3,7,8-TCDD is classified as a human carcinogen or as a probable human carcinogen. As Dr. Eaton says in his slides, "Committee felt that it really was not important, as TCDD will (and should) be regulated as if it is carcinogenic to humans regardless of what label it is given." Furthermore, Dr. Eaton says: "Overall, the committee concurs with the value of conducting analyses of total cancers given the potential for dioxin to affect multiple types of cancer." Thus, the attempt in the HHRA to cast doubt on this finding (e.g., "lack of consistency among specific tumor studies," should be ignored.

4.4.2.4, p.4-111-113. A non-linear model for assessment of carcinogenicity of dioxins is not available. IP seems to make the assumption that such a model would result in a lowering of calculated cancer risks. This is not yet determined. In view of the existing

body burden in the population, it is entirely possible that a non-linear model could lead to higher calculated risks. This section is irrelevant for current decision-making.

4.4.2.5, p. 4-113-114. IP reviews the criticisms of EPA's decision to use an ED01 as a point of departure (POD) for calculating cancer potency. IP also concurs with the NAS suggestion that EPA review the NTP animal bioassay (not available when EPA did its reassessment). Again, it is unclear how changing the POD or reviewing the NTP study will affect the determination of a potency slope, so this is irrelevant for current decision-making.

4.4.2.6, p. 4-115-117. IP reviews recent papers suggesting that the human-derived cancer potency estimate of 1E+6 is too high because half-life assumptions used to back calculate original exposures are too long. However, the papers cited need critical review by EPA and public health agencies before their conclusions can be accepted by regulatory and other government agencies entrusted with protecting public health. The DeVito slides suggest that this is underway, and that the issues are more complex than depicted in the *HHRA*. The section is irrelevant for current decision-making.

Risk Characterization

The risk characterization is not useful for regulatory decision-making because the pre-interim action conditions are not considered. It is not useful because fish consumption is not included in the exposure scenarios. It is not useful because of the exclusion of important data.

4.5, p. 4-126. The conclusion that concentrations of contaminants in fish are not higher than concentrations of these chemicals in background reference lakes is wrong.

4.5.1.1., p. 4-128. It is unjustified to assume that mixing of the top foot yard soil results in lower surface dioxin concentrations. It is very troubling that IP has dismissed germane data in the HHRA. For example soil sample EPA 2001 RES-16 was excluded "because the property burned down" (see table 2-1). Why are samples RES-16, RES-16A, and RES-16B missing from the hazard index risk summary table for past pre-IRM conditions table (see table D4-7a)? There were residents living on the property in the past and RES-16 is representative of the pre-IRM conditions. How can sample RES-16A pose the maximum noncancer hazard if the other samples appear to have higher contaminant concentrations (see table below)?

Sample	TEQdf (ppt) nd=0	PAH data	PCP (ppb)
RES-16 (EPA, 2001)	485	yes	1900
RES-16A (IP, 2003)	287	No data	No Data
RES-16B (IP, 2003)	48	No data	No Data

4.5.1.1, p. 4-128. "Consumption of homegrown produce was not considered for current conditions because there are no gardens grown in unamended soil." Again, the workplan requires that homegrown produce be considered in the risk assessment. Again, assessment under "current conditions" is deficient. A remedial action is done to protect public health and the environment for all relevant future uses. Houses burning down, inadequate 4 inch ground covers, etc. are irrelevant.

4.5.1.2. , p. 4-130. The following statement illustrates the degree of data manipulation and opacity of hazard and risk calculations in the *HHRA*: "The higher the pre-IRM soil concentrations, the greater the degree of hazard reduction achieved by the IRM. For both children and adults, the current hazard index at the location with minimum pre-IRM soil concentrations (RES-05) is 30% of the pre-IRM value (Table 4-16). The current hazard index at the location with the maximum pre-IRM soil concentration that also underwent interior house cleaning (RES-09) is 0.4 percent of the pre-IRM value." Are we therefore to assume that hazard indices are underestimated by factors between 3.3 and 250? These numbers highlight the lack of transparency in the risk calculations: based on the dilution factors described in the *HHRA* one would not expect these pre-post differences.

MDH suggests that EPA disregard IP's calculations of hazard indices from exposure point concentrations. EPA should utilize the original, pre-interim action data, and calculate soil concentration that yields a hazard index of 0.05, 0.1, 0.2 and 1.0.

4.5.1.3, p. 4-131. Conclusions for Area B non-cancer hazards do not reflect consumption of fish. They do not adequately reflect hazards to an individual spending most of their time in the Fox Creek area.

4.5.1.4, p. 4-132-133. Conclusions for Area A/B combined do not reflect fish consumption or pre-interim action conditions. They do not adequately reflect hazards to an individual spending most of their time in the Fox Creek area.

4.5.2.1, p. 4-135. Not considering consumption of homegrown produce because there are no current gardens is contrary to the workplan. Further, comments regarding houses that burned down, are tax-forfeited or opted out of the interim action are irrelevant for risk assessment. However, these comments are relevant for decision-making because they are indicative of the fact that this entire area is blighted and that the population is disadvantaged in many ways.

4.5.2.2, p. 4-137. The following statement illustrates the degree of data manipulation and opacity of hazard and risk calculations in the *HHRA*: "For both tribal and standard residents, the current cancer risk at the location with the minimum pre-IRM soil concentrations (RES-05) is 8 percent of the pre-IRM value (Table 4-16). The current cancer risk at the location with the maximum pre-IRM soil concentrations (RES-09) is 1 percent of the pre-IRM value." Are we therefore to assume that cancer risks (using the

old potency slope of 1.5 E+5/(mg/kg-d) are underestimated by factors between 12.5 and 100? These numbers highlight the lack of transparency in the risk calculations: based on the dilution factors described in the *HHRA* one would not expect these pre-post differences.

MDH suggests that EPA simply ignore IP's calculations of cancer risks from exposure point concentrations. EPA should go back to the original, pre-interim action data, and calculate soil concentrations that yield cancer risks of 1E-6, 1E-5, 1E-4. This should be done using the higher potency slope for reasons described above.

4.5.2.3, p. 4-138-140. Consumption of fish needs to be included in cancer risks from Area B and combined Area A/B.

4.5.4, p. 4-142; 4.5.5, p. 4-145-146. The statement is made that non-dietary exposure sources for the general population (soil, air and water), constitute only about 5 percent of total dioxin exposure. The State of Minnesota default policy for evaluation of non-cancer hazards from exposures to contaminated soil is that a relative source contribution of 20% should be used. MPCA Soil Reference Values for non-cancer endpoints are thus based on a hazard index of 0.2. Furthermore, IP notes that upper end background exposures for the general adult population are about 1.1 pg/kg-d (above the ATSDR MRL); average intakes are at 0.61 pg/kg-d (61% of the MRL). Childhood exposure is said to be as high as 2.2 pg/kg-d. In the case of soil contaminated with dioxins, a good case can be made that the remediation goal should be based on a hazard index below 0.2: perhaps 0.1 or even 0.05.

4.5.5, p. 4-144. "The primary reservoirs, sediment and soil, act as environmental sinks from which the highly persistent dioxins/furans compounds may be reintroduced into the food chain." This is a good argument for cleaning up the site.

4.6.1.1, p. 4-152. The following IP assumption is highly uncertain and not justifiable:

> "EPCs for soil excluded subsurface soil data because the subsurface data set is smaller than the surface data set and because subsurface sample locations were selected in a biased fashion at locations with high surface concentrations so that they probably overestimate typical subsurface concentrations. At most locations where both surface and subsurface soil samples were collected, surface concentrations are higher than subsurface concentrations, so activities that mix surface and subsurface soil would tend to decrease concentrations remaining at the surface."

Conclusions and Recommendations

1. The interim actions should not be used in the risk assessment, per letters from MDH (Patricia Bloomgren, 2003; Rita Messing and Daniel Peña, 2005).
2. Fish consumption should be included in the risk assessment.

3. IP's calculations cannot be used without extensive checking and modification.
4. EPA should complete a set of tables for cancer and non-cancer risks at different concentrations of soil dioxins using agreed-upon exposure factors. These should be used in conjunction with risks from exposures to sediments, groundwater, surface water and fish.
5. To the extent that particular exposures are not quantitatively considered (e.g., surface deposition onto leafy plants, groundwater and surface water exposures, eating fish eggs), these should be considered as uncertainties that will increase calculated risks.
6. To the extent that gaps in sampling data cannot be quantitatively considered (e.g., lack of characterization of sub-surface soil, lack of data for PAH's), these should be considered as uncertainties that will increase calculated risks.
7. To the extent that general environmental factors are not considered (e.g., lack of paved roads, and dusty environmental conditions), these should be considered as a source of underestimation of exposures to soil and dust.
8. EPA should acknowledge that some parameters (e.g., bioavailability of dioxins in dust particles, soil adherence factors, etc.) may be underestimated, and should be considered as resulting in an underestimation of risk.
9. EPA should acknowledge that many individuals in the area are long term residents, who may have had much larger exposures in the past. These exposures probably occurred across generations.
10. EPA should acknowledge State of Minnesota and Tribal risk assessment policies for assessment of cancer and non-cancer hazards and risks, and set remediation goals to determine further site investigation and remedial actions that are consisten with these policies.
11. EPA should act quickly to complete the risk assessment, establish conservative remediation goals, and proceed to complete site investigation and cleanup.

MDH has repeatedly made these or similar comments. From the beginning, MDH has sought to emphasize that this site is a blighted area on reservation land in the middle of a small city with many tribal members and people living in poverty. It is an urgent environmental justice issue and the timeline for action is entirely too long. MDH also reminds EPA that State of Minnesota dioxin policies have guided the risk assessment and cleanup of the Joslyn NPL site. EPA has used conservative criteria for cleanup of the Escambia site in Florida and for assessing dioxin risks at the World Trade Center. Use of State or Tribal policies and criteria for investigation and cleanup of this site has ample precedent and is consistent with existing laws and policies that guide EPA actions. In June 2007, John Linc Stine, Director of the Division of Environmental Health wrote to Richard Karl, Director of the Superfund Division, EPA Region 5 as follows:

"The situation for residents living on or near the site is little changed from what it was in 1995." Mr. Stine further went on to say: "It is time to implement a comprehensive site investigation and remedial action at the site. Criteria for dioxin soil remediation are available that are protective of public health. Minnesota has used a criterion of 35

ppt for remediation of soils in industrial areas at the Joslyn site...(the Minnesota criterion for residential soils is 20 ppt). EPA agreed to remediate soils at the Escambia site in Pensacola, Florida using the Florida criteria of 30 ppt for industrial areas and 7 ppt for residential areas."

In March 2005, Dianne Mandernach, Commissioner of the Minnesota Department of Health, wrote to Mr. Karl:

"Most of the people living in the impacted area are tribal members, many living in poverty. As a result, we believe that this site poses an urgent environmental justice concern."

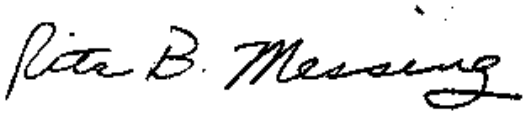
At the December 2006 National Environmental Public Health Conference in Atlanta, GA, Dr. Howard Frumkin, Director, NCEH/ATSDR made the following remarks at the opening plenary session (http://www.cdc.gov/nceh/conference/NEHC%20Transcripts%20Edited_v2.pdf):

"Next, we need to pursue justice. We know across the public health world, including in environmental public health, that not all of us are equally affected by public health problems. Some people are disproportionately exposed and disproportionately at risk. This has given rise to the transformative field of environmental justice. Poor communities and communities of color have taught us all that people at risk deserve special consideration."

MDH letters to EPA, MDH's dioxin risk assessment policies and the slide presentations of Drs. Eaton and DeVito are attached for your convenience.

Sincerely,

Patricia McCann



Rita Messing

Daniel Peña

Virginia Yingling

Minnesota Department of Health, Division of Environmental Health

References

1. Minnesota Pollution Control Agency (MPCA), Five-Year Review Report St. Regis Paper Company Site Cass Lake Minnesota March 27, 1995.
2. U.S. EPA Region 5, Second Five-Year Review Report St. Regis Paper Company Site Cass Lake, Cass County, Minnesota September 2000.
3. Third Five-Year Review Report St. Regis Paper Company Site Cass Lake, Cass County, Minnesota September 2005.
4. U.S. EPA Region 5. Data Evaluation Report, for the St. Regis Paper Company Site, Cass Lake, Minnesota. August 23, 2002
5. U.S. EPA. Unilateral Administrative Order, V-W-'04-C-771 (Residential Soil Removal Action), Pursuant to Section 10 CERCLA, Sept 19, 2005.
6. MPCA, Memorandum: Soil Reference Value Updates, September 7,2005
7. MDH Risk Assessment webpage, Methods for Estimating the Carcinogenic Health Risks from Dioxin-Like Compounds (http://www.health.state.mn.us/divs/eh/risk/guidance/dioxinmemo1.htm l). Updated October 2006
8. ATSDR, St. Regis Paper Company Health Consultation, August 2004.
9. MDH Letter to William Muno EPA Director Superfund Division: Removal Action Plan October 28, 2003.
10. MDH letter to Tim Drexler EPA Remedial Project Manager: Interim House Dust Plan. June 23, 2005.

Certification

The Minnesota Department of Health prepared this Health Consultation Letter evaluation of the St. Regis Superfund Site, under a cooperative agreement with the Agency for Toxic Substances and Disease Registry (ATSDR). At the time this Health Consultation Letter was written, it was in accordance with the approved methodologies and procedures. Editorial review was completed by the Cooperative Agreement partner.

Technical Project Officer, Cooperative Agreement Team, CAPEB, DHAC, ATSDR

The Division of Health Assessment and Consultation, ATSDR, has reviewed this public health consultation and concurs with the findings.

Team Leader, Cooperative Agreement Team, CAPEB, DHAC, ATSDR

Attachment 1
MDH Dioxin Toxicity Assessment Policy

Minnesota Department of Health
Protecting, maintaining and improving the health of all Minnesotans

Risk Assessment
Rules/Guidance

The following guidance was developed by the Minnesota Department of Health (MDH) at the request of the Minnesota Pollution Control Agency (MPCA). For more information, contact the Health Risk Assessment Unit, 651/201-4899. For more information about dioxin health risks, see Development of Inhalation Benchmark for Dioxin-Like Compounds and Facts about Dioxin.

Methods for Estimating the Carcinogenic Health Risks from Dioxin-Like Compounds
Updated October 2006

The Minnesota Department of Health (MDH) prepared this guidance in response to a request in 2003 from the Minnesota Pollution Control Agency (MPCA), and to identify a consistent approach for agencies and programs to assess the carcinogenic health risks from exposure to dioxin-like compounds. Guidance for assessing the noncancer health risks is still under development and will not be addressed in this memo. Because of the uncertainties associated with the toxicities of dioxin mixtures, MDH uses a conservative approach to evaluate potential risks. As more data become available, MDH re-evaluates and revises its risk assessment methods and procedures, as appropriate.

Dioxin-like Compounds

The term "dioxins" is used to refer to a family of complex but related chlorinated compounds with similar chemical structures and biological activity. The polychlorinated dibenzo-p-dioxins (PCDDs) include 75 individual compounds, the polychlorinated dibenzofurans (PCDFs) include 135 individual compounds, and the polychlorinated biphenyls (PCBs) include 209 individual compounds. These individual compounds are technically referred to as congeners. Based on their ability to bind to the Ah receptor and evoke a response 7 of the 75 PCDD congeners (i.e., those with chlorine substitutions in the 2,3,7, and 8 positions), 10 of the 135 PCDF congeners (i.e., those with chlorine substitution in the 2,3,7, and 8 positions), and 12 of the 209 PCB congeners (those containing 4 or more chlorines with 1 or no substitutions at the ortho position) are thought to have significant dioxin-like toxicity. The 29 compounds identified as having significant dioxin-like toxicity concerns are identified in Table 1.

Toxic Equivalence Factors (TEFs)

Dioxins interfere with a basic and ubiquitous receptor system (the Ah receptor) that regulates enzymes and other proteins. While it is believed that these 29 compounds have a similar mechanism of toxicity not all are equally toxic. The most toxic and best-studied dioxin is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). The remaining 28 compounds have been assigned toxicity values relative to 2,3,7,8-TCDD. These relative toxicity values are called toxicity equivalence factors (TEFs). 2,3,7,8-TCDD is assigned a TEF of 1 and the remaining compounds are typically assigned values less than 1. The Minnesota Department of Health (MDH) recommends utilization of the World Health Organization's (WHO) 2005 TEF scheme (TEF_{WHO05}) (Van den Berg, et al., 2005) to weight each compound according to its relative toxicity for cancer risk evaluations. The TEF_{WHO05} values are shown in Table 2.

The compound specific TEF describes an order of magnitude consensus estimate derived from scientific judgment based on the examination of available experimental data. TEF estimates are generated from several sources of experimental data. The resulting range of relative potency values derived from the individual experiments for a particular compound are variable. The TEFs were primarily derived from in vivo toxicity data, which were given more weight than the in vitro and/or quantitative structure-activity relationship data. The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds (Van den Berg et al. 2005) should be referred to for additional information on the determination and validation of the $TEFs_{WHO05}$.

The United States Environmental Protection Agency (U.S. EPA) as well as several states, countries and international agencies have adopted the WHO 2005 TEF scheme. Utilization of the WHO 2005 TEF scheme will facilitate the comparison of environmental measurements to national and international databases.

Toxic Equivalent Concentration Calculation (TEQ)

The dioxin-like compounds exist in the environment as mixtures (i.e., a single compound is not found in isolation). Because dioxins differ in their toxic potential or potency, the toxicity of each component of the mixture must be accounted for in estimating the overall toxicity of the mixture. The evaluation of environmental dioxin mixtures consists of three simple steps. The first is a laboratory measurement of the concentration of each individual compound. Then, the measured concentration of each compound is multiplied by its corresponding TEF to produce a TCDD toxicity equivalent (TEQ) concentration. Finally, the TEQ concentrations for each compound are added together with the TEQs for each of the other compounds present to determine the total TCDD TEQ concentration in the sample. The total TCDD TEQ concentration represents the amount of 2,3,7,8-TCDD alone, that it would take to equal the combined toxic effect of the mixture.

The variability in relative potency values for individual compounds mentioned above may not significantly impact an individual risk estimate. According to the U.S. EPA draft reassessment only 5 compounds (2,3,7,8-TCDD, 1,2,3,7,8-PentaCDD, 1,2,3,6,7,8-HexaCDD, 2,3,4,7,8-PentaCDF, and PCB 126) account for 70 to 80 percent of the TCDD TEQ in the human body and food products. The relative potency variability reported in the literature for these 5 compounds is much lower than for other compounds (U.S. EPA 2000).

A number of studies have examined the toxicity of complex mixtures of dioxins and non-dioxin-like compounds in the laboratory. Some of these studies have compared the predicted (TEQ) toxicity of a mixture to the actual measured toxicity of that mixture. Other studies have compared the toxicity of individual compounds to those of the mixture in the same test system. Mixtures tested include both laboratory mixtures of individual compounds and environmental samples.

The TEF/TEQ methodology addresses the toxicity potential of complex mixture in terms of an equivalent mass of 2,3,7,8-TCDD. Although the various congeners of a mixture have relative equivalent toxicity to 2,3,7,8-TCDD, these congeners may not have the same pharmacokinetics and do not necessarily share the same environmental fate as 2,3,7,8-TCDD. The impact of an environmental mixture will likely also be affected by the ability of our bodies to absorb, metabolize and excrete the individual congeners from the environmental media (e.g. soil). For some risk assessments the differences in fate and transport of different congeners must be taken into consideration and TEQs calculated at the point of exposure to achieve more accurate assessments.

Although the use of TEFs and the TEQ approach is widespread, its use is not without controversy. The WHO has suggested that the TEF scheme and the TEQ methodology be re-evaluated every 5 years to account for new scientific information. The WHO completed their most recent review of the TEFs and TEQ methodology in 2005 (Van den Berg et al., 2005). In this review they reaffirmed the use of TEFs as the best available tool for estimating the health risk of exposures to complex mixtures of dioxin-like chemicals.

Quantitative Cancer Risk Assessment

Cancer Classification:

The MDH, U.S. EPA, National Toxicology Program (NTP) and the International Agency for Cancer Research (IARC) have characterized 2,3,7,8-TCDD as a "human carcinogen". The MDH and the U.S. EPA have classified the complex mixtures of dioxin to which people are exposed as a "likely human carcinogen". The degree of certainty of the cancer hazard is dependent on the major constituents of the mixture. The consistent, suggestive evidence from epidemiology studies combined with the unequivocal evidence in animal studies and inferences drawn from mechanistic data support the characterization of complex mixtures of dioxin and related compounds as "likely" cancer hazards. "Human carcinogen" and "likely" are descriptors which are consistent with the U.S. EPA draft final cancer guidelines (U.S. EPA 2003). They are roughly equivalent to the terms "known" and "probable" human carcinogen contained in earlier U.S. EPA cancer guidelines (U.S. EPA 1986).

Oral Cancer Slope Factor:

The U.S. EPA's draft dioxin reassessment efforts produced two upper bound slope factors for estimating human cancer risk from exposure to dioxins:

1×10^{-3} (pg TCDD TEQ/ kg body weight/day)$^{-1}$ based on an evaluation of the human epidemiology data and 1.4×10^{-3} (pg TCDD TEQ/kg body weight/day) $^{-1}$ based on a re-evaluation of the animal data (liver cancer in female rats).

The actual shape of the low-dose exposure-response relation for animals or humans cannot be determined from the available data. For this reason U.S. EPA utilized a linear dose extrapolation model to derive an upper bound cancer potency factor. The true risk is unknown but is likely to be lower.

The MDH believes that exposure to ("known" or "likely") carcinogens should be minimized where possible; this is especially true for dioxins due to existing body burden estimates. When a numerical cancer slope factor is needed to evaluate incremental risk, MDH recommends utilizing an interim cancer slope factor of 1.4×10^{-3} (pg TCDD TEQ/kg body weight/day) $^{-1}$ (i.e., 1.4×10^{6} per mg TCDD TEQ/kg/day). This value is based on EPA's draft animal-based cancer slope factor. Concerns about the quality of the exposure estimates in the human epidemiological studies preclude the quantitative use of these data in developing a cancer potency slope for dioxin; however, the results from modeling the human studies are consistent with the cancer potency slope derived by modeling data from animal studies.

As noted above, the recommended interim cancer slope factor is based on information contained in the EPA 2003 draft dioxin reassessment. The National Research Council (NRC) of the National Academies has recently completed a comprehensive review of the EPA 2003 draft assessment. The NRC report contained conclusions and recommendations on how the EPA 2003 draft reassessment could be improved. The MDH is initiating a review of the NRC report as well as other relevant scientific data generated since the draft reassessment (e.g., the chronic

toxicological study conducted by the National Toxicology Program). The MDH does not recommend any changes to its guidance at this time.

The recommended slope factor is derived from the same study, Kociba et al., 1978, as the previous slope factor estimate (1.56E+5 per mg/kg/day). The development of the recommended slope factor utilized current methods of analysis, including the use of body burden as the dose metric for animal-to-human dose equivalence calculations (i.e., adjustments to account for the differences in half-life of dioxins in the bodies of laboratory animals and humans), and a re-evaluation of the liver tumors in the Kociba study using the latest pathology criteria.

Inhalation Unit Risk Factor:

For bioaccumulative compounds such as the dioxins the primary exposure route of concern for long-term or chronic toxicity is ingestion rather than inhalation. Toxicological data from inhalation studies is not available for the dioxins. As stated in the MDH Statement of Need and Reasonableness (SONAR) for the Health Risk Values (HRVs) chronic ingestion studies are not, as a rule, utilized by the MDH to develop inhalation HRVs. Route-to-route extrapolation may be appropriate when sufficient toxicokinetic information is available and the critical effect would be the same regardless of how the toxicant is administered.

There is adequate evidence, in laboratory animals, that 2,3,7,8-TCDD is a multisite carcinogen capable of increasing the incidence of tumors at sites distant from the site of treatment. The limited epidemiologic evidence from occupationally exposed workers is also consistent with increased cancer risk at multiple sites.

The situations where extrapolation from an oral exposure to an inhalation exposure is inappropriate are also discussed in the SONAR:

"There are, however, situations where this extrapolation technique is inappropriate. For instance, if the critical effect is specific for the respiratory system, or if the toxicity of a chemical is expressed at or near the site of application, data from oral exposure should not be used to extrapolate to an inhalation exposure. Another case where extrapolation would be inappropriate is when the target organ for the critical effect is the liver. The liver, because of its unique structure and circulation, is subjected to much higher concentrations of ingested chemicals than other organs. In addition, the unique biochemistry of the hepatocytes can result in the generation of very different metabolic products of a toxicant in the liver than would be produced in other organs. For these reasons an extrapolation approach will not be used if the liver is the target organ for a toxicant following oral exposure."

The liver is a target organ of dioxin toxicity and the recommended oral slope factor is based on liver tumors. The MDH HRV staff were consulted regarding interpretation of the SONAR and the appropriateness of utilizing route-to-route extrapolation for dioxins. 2,3,7,8-TCDD and dioxin-like compounds undergo limited metabolism and exhibit long half-lives in the body. As a result the liver would not be subjected to significantly higher concentrations or significantly different metabolic products than other organs. Therefore, although the recommended oral slope factor is based on liver tumors, route-to-route extrapolation is acceptable.

In order to extrapolate an inhalation unit risk factor from the oral slope factor an absorption adjustment factor, inhalation rate, and body weight are necessary. These parameter values are influenced by the physical form of dioxins (e.g., particulate or vapor-phase) and the individual or population under evaluation. MDH will not recommend default adjustment factors, inhalation rates or body weights at this time. As more data become available, MDH will re-evaluate this

position and revise its recommendation as appropriate.

Information contained in the U.S. EPA draft dioxin reassessment may be a useful source of information for the MPCA. Part I, Volume 3, Chapter 4 and Volume 4, Chapter 2 of the U.S. EPA's draft reassessment provide guidance for estimating potential risks from a variety of exposure pathways, including the inhalation pathway.

Utilizing animal data and information on fate of particles in the respiratory system, U.S. EPA estimated that the fraction of 2,3,7,8-TCDD absorbed into the body ranges from 0.25 to 0.29. Although the rate of absorption of vapor-phase 2,3,7,8-TCDD into the lungs has not been studied, the U.S. EPA concluded that it seems reasonable to assume that the absorption in the vapor phase should exceed that of absorption from bound 2,3,7,8-TCDD on particulates, probably above 50%. Given the paucity of data U.S. EPA recommended that assessors not attempt any such adjustments at this point, but fully acknowledged the uncertainty. Absorption correction factors were recommended for use in the soil ingestion and soil dermal contact pathways.

A variety of inhalation rates and body weights were utilized by the U.S. EPA to estimate inhalation exposure. The specific value selected depended on the age of the subpopulation of concern and whether a central tendency or upper tendency estimate was desired.

Table 1. List of Compounds With Varying Dioxin-like Toxicity

Chlorinated Dibenzo-p-dioxins (CDDs)	**Chlorinated Dibenzofurans (CDFs)**	**Polychlorinated Biphenyls (PCBs)**
2,3,7,8-TCDD	2,3,7,8-TetraCDF	3,3'4,4'-TetraCB (PCB 77)
1,2,3,7,8-PentaCDD	1,2,3,7,8-PentaCDF	3,4,4',5-TetraCB (PCB 81)
1,2,3,4,7,8-HexaCDD	2,3,4,7,8-PentaCDF	2,3,3',4,4'-PentaCB (PCB 105)
1,2,3,6,7,8-HexaCDD	1,2,3,4,7,8-HexaCDF	2,3,4,4',5-PentaCB (PCB 114)
1,2,3,7,8,9-HexaCDD	1,2,3,6,7,8-HexaCDF	2,3',4,4',5-PentaCB (PCB 118)
1,2,3,4,6,7,8-HeptaCDD	2,3,4,6,7,8-HexaCDF	2',3,4,4',5-PentaCB (PCB 123)
1,2,3,4,6,7,8,9-OctaCDD	1,2,3,7,8,9-HexaCDF	3,3',4,4',5-PentaCB (PCB 126)
	1,2,3,4,6,7,8-HeptaCDF	2,3,3',4,4',5-HexaCB (PCB 156)
	1,2,3,4,7,8,9-HeptapCDF	2,3,3',4,4',5'-HexaCB (PCB 157)
	1,2,3,4,6,7,8,9-OctaCDF	2,3',4,4',5,5'-HexaCB (PCB 167)
		3,3',4,4',5,5'-HexaCB (PCB 169)
		2,3,3',4,4',5,5'-HeptaCB (PCB 189)

Table 2. WHO_{05} Toxic Equivalent Factors

Compound	**TEF_{WHO05}**
CDDs	
2,3,7,8-TetraCDD	1
1,2,3,7,8-PentaCDD	1
1,2,3,4,7,8-HexaCDD	0.1
1,2,3,6,7,8-HexaCDD	0.1
1,2,3,7,8,9-HexaCDD	0.1
1,2,3,4,6,7,8-HeptaCDD	0.01
1,2,3,4,6,7,8,9-OctaCDD	0.0003
CDFs	

2,3,7,8-TetraCDF	0.1
1,2,3,7,8-PentaCDF	0.03
2,3,4,7,8-PentaCDF	0.3
1,2,3,4,7,8-HexaCDF	0.1
1,2,3,6,7,8-HexaCDF	0.1
2,3,4,6,7,8-HexaCDF	0.1
1,2,3,7,8,9-HexaCDF	0.1
1,2,3,4,6,7,8-HeptaCDF	0.01
1,2,3,4,7,8,9-HeptaCDF	0.01
1,2,3,4,6,7,8,9-OctaCDF	0.0003
PCBs	
3,3'4,4'-TetraCB (PCB 77)	0.0001
3,4,4',5-TetraCB (PCB 81)	0.00003
2,3,3',4,4'-PentaCB (PCB 105)	0.00003
2,3,4,4',5-PentaCB (PCB 114)	0.00003
2,3',4,4',5-PentaCB (PCB 118)	0.00003
2',3,4,4',5-PentaCB (PCB 123)	0.00003
3,3',4,4',5-PentaCB (PCB 126)	0.1
2,3,3',4,4',5-HexaCB (PCB 156)	0.00003
2,3,3',4,4',5'-HexaCB (PCB 157)	0.00003
2,3',4,4',5,5'-HexaCB (PCB 167)	0.00003
3,3',4,4',5,5'-HexaCB (PCB 169)	0.03
2,3,3',4,4',5,5'-HeptaCB (PCB 189)	0.00003

References

CalEPA. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (OEHHA). Air Toxics Hot Spots Program Risk Assessment Guidelines, Part II: Technical Support Document for Describing Available Cancer Potency Factors, December 2002. Chlorinated Dibenzo-p-Dioxins and Chlorinated Dibenzofurans, pp. 167 - 187. http://www.oehha.ca.gov/air/hot_spots/pdf/TSDNov2002.pdf

Minnesota Department of Health (MDH) Statement of Need and Reasonableness, Proposed Permanent Rules Relating to Health Risk Values, Minnesota Rules, Parts 4717.8000 to 4717.8600, August 10, 2001.

NTP. Report on Carcinogens, Tenth Edition: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, December 2002. http://ehp.niehs.nih.gov/roc/toc10.html

U.S. EPA, 1986. United States Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Published in the Federal Register 51(185): 33992 - 34003, September 24, 1986. http://www.epa.gov/ncea/raf/car2sab/guidelines_1986.pdf

U.S. EPA, 2000. United States Environmental Protection Agency. Draft Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin TCDD) and Related Compounds. Draft Final, September 2000. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55265

U.S. EPA, 2003. United States Environmental Protection Agency. Draft Final Guidelines for Carcinogen Risk Assessment. February 2003. EPA/630/P-03/001A.

http://www.epa.gov/ncea/raf/cancer2003.htm

Van den Berg, M, L. Birnbaum, et al., The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds. Toxicological Sciences, October 2006; 93:223-241

WHO, World Health Organization. Executive Summary - Assessment of the Health Risks of Dioxins: Re-evaluation of the Tolerable Daily Intake (TDI), WHO Consultation, May 25 - 29, 1998, Geneva, Switzerland. http://www.who.int/fsf/Chemicalcontaminants/whoinfo.htm

For questions about this page, please contact our Environmental Health Division: ehweb@health.state.mn.us

Updated Wednesday, 14-Mar-2007 11:57:55 CDT

Attachment 2
MDH Letters to EPA Superfund Division Director

MINNESOTA MDH DEPARTMENT OF HEALTH

June 27, 2007

Protecting, maintaining and improving the health of all Minnesotans

Richard Karl, Director
Superfund Division
EPA Region 5
77 West Jackson Blvd. Mail Code S-6J
Chicago, IL 60604

Dear Mr. Karl:

I am writing to express concern with the lack of progress in remediation of the St. Regis Paper Co. National Priorities List (NPL; superfund) site in Cass Lake, MND067597940.

The situation for residents living on or near the site is little changed from what it was in 1995 when EPA reviewed and approved the Five-Year Review Report developed by the Minnesota Pollution Control Agency (MPCA)[1]. That review noted the needs for further response actions to contain the groundwater contamination plume, define existence and/or extent of LNAPL (light non-aqueous phase liquid) and DNAPL (dense non-aqueous phase liquid) in surficial aquifers, install additional monitoring wells, and address residual soil contamination. Our remarks below are mainly concerned with soil contamination because that is the most prominent current source of human exposure. However, we also believe that other important issues that were identified over ten years ago are still not fully addressed.

Work on a human health and ecological risk assessment for this site has been ongoing since early 2003. A work plan was completed in early 2004 and a draft risk assessment was submitted to EPA by International Paper in November 2005. The risk assessment was not adequate and International Paper was told by EPA to make extensive revisions. In the draft document, International Paper arbitrarily excluded environmental data collected by the EPA and the Leech Lake Band of Ojibwe, used an incorrect reference dose to assess toxicity of dioxin for children, used exposure factors for soil which were not approved by EPA, used invalid methodology for assessment of site-related fish contamination, failed to provide any justification for their chosen dioxin bioavailability factor, failed to provide parallel cancer risk calculations based on both older and more modern cancer potency slopes for dioxins, failed to acknowledge State of Minnesota standards and guidelines for hazardous chemical contamination and exposures, and failed to adequately assess uncertainties in the risk assessment especially with regard to unexamined subsurface contamination. Numerous other more minor deficiencies were also noted.

Despite a great deal of correspondence, conference calls and meetings, over 18 months later we still do not have a human health and ecological risk assessment for the site. In the meantime, an inadequate removal action has occurred, removing only soil containing over 1,000 part per trillion (ppt) of dioxin in a patchwork of areas throughout the site, down to a depth in many locations of as little as three inches. Soils with high levels of dioxin contamination remain accessible on the site. Further, although there is an interim remedy to reduce indoor dust exposure by cleaning peoples' houses and providing some assistance with ground cover for yards, the area remains very dusty. For example, the roads are unpaved, and high levels of dioxins remain in other unvegetated areas in close proximity to houses.

It is time to implement a comprehensive site investigation and remedial action at the site. Criteria for dioxin soil remediation are available that are protective of public health. Minnesota has used a criterion of 35 ppt for remediation of soils in industrial areas at the Joslyn site in Brooklyn Center, Minnesota (the Minnesota criterion for residential soils is 20 ppt)[2]. EPA agreed to remediate soils at the Escambia site in Pensacola, Florida using the Florida criteria of 30 ppt for industrial areas and 7 ppt for residential areas[3]. Further, additional sampling and investigation of soils, sediments and fish is needed to develop a reliable picture of contamination at the site consistent with health protective cleanup down to low levels of dioxins and remove various deficiencies in each others' environmental data that have been identified by EPA, the Leech Lake Band and International Paper. Delaying these activities until completion of a risk assessment by International Paper is a strategy that has proved to be impossible to execute in a timely manner and may be impossible to ever execute.

Recently, the Minnesota Pollution Control Agency (MPCA) sent you a letter expressing some of the same concerns about the site investigation[4], especially regarding the lack of examination of soil contamination above "Tier 1" screening values (i.e., 20-35 ppt) at depth, and the necessity to apply a remedy to depths of 4 to 10 feet. It seems to us that the risk assessment depends upon environmental data; lack of such data will entail very large uncertainties in risk estimates. As you are aware, when there are uncertainties it is MDH policy to assume that risks are higher rather than lower or "best estimates."

We also want to endorse and support the MPCA request[4] that you have a discussion with the Leech Lake Band of Ojibwe (LLBO) about tribal jurisdiction and tribal cleanup criteria on reservation lands. As noted by the MPCA, a discussion is needed about how the LLBO can affect remedy selection and implementation.

We therefore request that EPA identify and execute a strategy to complete the site investigation, and to set and achieve remediation goals in a prompt and timely manner, taking into account state and tribal regulations and policies. This may require taking direct control of many activities at the site. We are, of course, open to any other strategy that can achieve the goal of public health protection within a reasonable time frame.

If you have questions or need further information about MDH involvement at this site please call me at (651)201-4675 or by e-mail at john.stine@health.state.mn.us.

Sincerely,

John Linc Stine, Director
Environmental Health Division
P.O. Box 64975
St. Paul, Minnesota 55164-0975

References

1. EPA/MPCA. Approval Letter from William E. Muno, EPA to James Warner, MPCA, March 1995; Five-Year Review Report, St. Regis Paper Company Site, March 1995.
2. MPCA. Memo from Dave Douglas, Preliminary Remediation Goals for the West Area of the Joslyn Manufacturing and Supply Company Superfund Site, June 2005.
3. EPA. Office of the Inspector General Ombudsman Report. Review of Actions at Escambia Treating Company Site, Pensacola, Florida. September 2004.
4. MPCA. Letter from Kathryn Sather to Wendy Carney, May 2007.

cc: The Honorable Tim Pawlenty, Governor
The Honorable Norm Coleman, U.S. Senate
The Honorable Amy Klobuchar, U.S. Senate
The Honorable James Oberstar, U.S. House of Representatives
The Honorable Mary A. Olson, Minnesota Senate
The Honorable Frank Moe, Minnesota House of Representatives
The Honorable George Goggleye, Chairman, Leech Lake Band of Ojibwe
The Honorable Wayne La Duke, Mayor, Cass Lake
Rich Robinson, Leech Lake Band of Ojibwe
Shirley Nordrum, Leech Lake Band of Ojibwe
Brad Moore, Commissioner, MPCA
Kathryn Sather, Director, MPCA Remediation Division
Wendy Carney, EPA
Sonia Vega, EPA
William Cibulas, Jr., ATSDR
Mark Johnson, ATSDR

6/23/05

MINNESOTA MDH DEPARTMENT OF HEALTH

Protecting, maintaining and improving the health of all Minnesotans

June 23, 2005

Tim Drexler
Remedial Project manager
EPA Region 5 (SR-5J)
77 W. Jackson Blvd.
Chicago, IL 60604-3590

Dear Mr. Drexler:

Minnesota Department of Health (MDH) staff are pleased to have the opportunity to comment on the US Environmental Protection Agency (EPA) interim plan for house dust contamination at the St. Regis Paper Company Superfund Site in Cass Lake, MN. MDH supports the EPA interim remedy for contaminated dust in homes on the St. Regis site. If implemented as designed the plan will reduce inhalation and dermal contact of residents to indoor dust. We do recommend that the interim action include use of HEPA filters in the homes, and be expanded to include any commercial establishments on the site. Exposures to people who work in such establishments could be comparable to residential exposures and should therefore be reduced as well.

We recommend that this action be accompanied by a plan for health communication in order to address community concerns. Residents will need to understand why house cleaners will wear protective gear, while residents have been living there for many years without protection. They will also need assurance that EPA is vigorously pursuing a remedial action for the site that will be consistent with the interim action. This means that EPA will need to acknowledge sources of soil exposures that the interim action does not cover. These include dirt roads and driveways and other areas that will continue to generate dust. Additionally, large areas of the site contain high concentrations of dioxins up to the removal criterion of 1,000 parts per trillion, and remain bare and accessible to the public. These areas are accessible to children, and pedestrians commonly traverse the site as they walk back and forth to the main business area of Cass Lake.

MDH believes that a final remedial action needs to use the same risk assessment methodology and criteria that are the basis for the dust plan. This will ensure that the remedial action will not result in a reversion to a higher level of exposure after the interim action ceases. This methodology is described in *World Trade Center Indoor Environment Assessment: Selecting Contaminants of Potential Concern and Setting Health Based Benchmarks*, May 2003 (available at www.epa.gov/wtc/copc_benchmark.pdf). This is a joint work of EPA, the New York City Department of Health and Mental Hygiene, the US Agency for Toxic Substances and Disease Registry (ATSDR), the New York State Department of Health and the US Occupational Safety and Health Administration (OSHA). The document employs a cancer slope factor of 1000000 $(mg/kg/day)^{-1}$, and standard exposure assumptions to arrive at a benchmark concentration for dioxins of 2 ng/m^2. We note that this is essentially equivalent to the screening concentration

specified in the document of 1.7 ng/m^2 for dioxin in settled dust. The report also specifies a screening level of 60 ng/kg (parts per trillion) of bulk dust. The document does not specify a default assumption for bulk dust density. However, these are equivalent if the bulk density of the dust is 28 g/m^2. Most sampled houses at the St. Regis site had a higher density of dust.

Further, MDH believes that it is important to carry out the interim plan in such a way that the ultimate remedial action is not compromised. The interim plan calls for covering and seeding residential yards. MDH recommends that the soil levels used to evaluate remedial actions not include the dilution caused by the interim action. Further, in order not to increase waste if soil is ultimately removed, or in order to warn that serious levels of contamination may exist at very shallow depth if soil is not removed, MDH recommends that a geosynthetic membrane or other barrier be placed between existing soils and the clean soils applied at the surface. Use of a barrier will also minimize cross contamination, although deposition of contaminated soil from nearby areas will likely still occur. We note that a remedial action should also take into account Minnesota laws and policies for residential, commercial or industrial use of land regarding depth to contaminated soil, deed restrictions, easements, etc.

Thank you for the opportunity to comment on this proposal, and your consideration of these suggestions. If you have questions please contact us.

Sincerely,

Daniel Peña, M.S.
Health Assessor
Site Assessment and Consultation Unit

Rita Messing, Ph.D.
Supervisor
Site Assessment and Consultation Unit

cc: Hon. Elaine Fleming, Mayor, Cass Lake
Shirley Nordrum, Leech Lake Band
Susan Johnson, MPCA
Mark Johnson, ATSDR
Jeffrey Kellam, ATSDR
Alan Yarbrough, ATSDR

March 2, 2005

MINNESOTA MDH DEPARTMENT OF HEALTH

Protecting, maintaining and improving the health of all Minnesotans

Richard Karl
Director, Superfund Division
US EPA Region 5
77 West Jackson Boulevard
Chicago, IL 60604

Re: MND057597940, St. Regis Paper Company, Cass Lake, Cass County, Minnesota

Dear Mr. Karl:

We are writing to you about evidence of ongoing residential exposures to dioxins in contaminated soil and dust in the vicinity of the St. Regis Paper Company facility, a former wood-treating facility, which operated from 1957 to 1985. The site was placed on the National Priorities List in 1984. The property is located on tribal land within the Leech Lake Band of Ojibwe Reservation.

A five-year review conducted in 1995 recommended further action to investigate and remediate the site, because remedial actions taken in the 1980's were not adequate. In 2000, at the beginning of the second five-year review process, US EPA initiated further site investigation that is still underway. To date, soil sampling efforts conducted on residential and non-residential properties in the vicinity of the former manufacturing area have found an area of soil contamination in excess of 50 ng/kg of dioxins (measured as toxic equivalents to 2,3,7,8 tetrachlorodibenzo-p-dioxin) covering a large portion of an area bounded by the Burlington Northern Santa Fe Railroad Tracks to the north, South Third Street to the south, Highway 371 to the west and a former landfill area to the east. There is also a small area of contamination north of the railroad tracks. (See the attached map from US EPA showing the estimated extent of contamination). Approximately 40 residences are located within or adjacent to the former manufacturing areas, and US EPA has found contamination greater than 50 ng/kg at more than10 residential properties (some samples are composites of more than one property). Some residential properties still have not been tested. Other contaminants, including arsenic and polycyclic aromatic hydrocarbons (PAHs) have also been found.

In 2004, the Minnesota Department of Health, the Leech Lake Band of Ojibwe and the US Agency for Toxic Substances and Disease Registry (ATSDR), published a Health Consultation reviewing the site soil contamination data. The document concluded that a cleanup goal for dioxin based on the ATSDR health based soil screening criterion of 50 ng/kg would be protective of public health. The Health Consultation also recommended that all residents south of the railroad tracks minimize contact with soils in their yards.

Under an EPA order, International Paper recently conducted indoor dust sampling at 10 properties, with a single composite sample collected from each home. The results showed that indoor dust concentrations exceeded 50 ng/kg of dioxins in six of the 10 homes. One of the residences serves as a child care provider. There was a very strong correlation between the indoor dust samples and the exterior soil samples in the yards. For a comparison to cleanup criteria for dioxins in dust used by US EPA, a dioxin concentration of 60 ng/kg and dioxin loading density of 2 ng/m^2 in dust was specified as a health-based criteria for re-occupancy of buildings impacted by emissions resulting from the destruction of the World Trade Center.

There are a number of reasons that make the dioxin exposure to this Leech Lake population significant and worthy of special consideration for taking action:

1) Most of the people living in the impacted area are tribal members, many living in poverty. As a result, we believe that this site poses an urgent environmental justice concern.

2) Many of these individuals are long-term residents who lived in the area during the operation of the wood treatment facility. As a result, they were likely to have had significant exposures over decades, perhaps across generations. In spite of initial site remediation actions in the early 1980s, exposure to dioxin-contaminated soil has continued to the present.

3) Due to the extensive environmental contamination in this area, this population has also been experiencing exposure through other pathways, especially from local food supplies.

4) The soil in this area is extremely sandy, with limited vegetative cover and unpaved roads. As a result, this is a very dusty environment. The use of air conditioning is rare so dust migration into indoor spaces is significant. Action that people may take to avoid contact with contaminated exterior soils does not eliminate exposures from occurring within their homes

5) In addition to dioxins, elevated levels of arsenic and PAHs from the wood treatment operation occur as contaminants in both exterior soil and indoor dust.

For these reasons, we strongly urge you to devise a plan to effectively eliminate the on-going exposures to the site contaminants. While a long-term remedy for the industrial site and impacted residential properties is being developed, immediate intervention in on-going exposures needs to be initiated either through remediation of contamination within the interior of impacted homes or relocation of the residents. Any plan should be developed in consultation with the affected community. In the past, USEPA has taken action to intervene in dioxin exposures of similar, if not lesser, magnitude. Thank you for your attention.

If you have questions or need further information, please contact Dr. Rita Messing of my staff at (651)215-0924 or by e-mail at rita.messing@state.mn.us.

Sincerely,

Dianne M. Mandernach

Dianne M. Mandernach
Commissioner
P.O. Box 64882
St. Paul, MN 55156-0882

cc: Bharat Mathur, Acting Regional Administrator, USEPA- Region 5
The Honorable Mark Dayton, US Senate
The Honorable Norm Coleman US Senate
The Honorable James Oberstar, US House of Representatives
The Honorable Carrie Ruud, Minnesota Senate
The Honorable Frank Moe, Minnesota House of Representatives
The Honorable Sheryl Corrigan, Commissioner, Minnesota Pollution Control Agency
The Honorable George Googleye Jr., Chairman, Leech Lake Band
The Honorable Elaine Fleming, Mayor of Cass Lake
Dr. Tom Sinks, Assistant Administrator, ATSDR

MINNESOTA
MDH
DEPARTMENT OF HEALTH

10/28/03

Protecting, maintaining and improving the health of all Minnesotans

October 28, 2003

William Muno
Director, Superfund Division
U.S. Environmental Protection Agency Region 5
77 West Jackson Boulevard
Chicago, Illinois 60604

Dear Mr. Muno:

We are writing to ask you to ensure that any removal action taken by the U. S. Environmental Protection Agency (EPA) at the St. Regis Paper Company, Cass Lake, Cass County, Minnesota Superfund Site (National Priorities List MND05759740) be protective of public health. In order for a removal action to contribute to protection of public health:

- Contaminated areas addressed in the removal action must be cleaned so that the public does not have access to contaminated soils; and
- The removal action should be taken so that it complements, rather than interferes with, any future remedial actions performed as a result of human health and ecological risk assessments.

It was our understanding, based on conversations with Sonia Vega, the EPA On Scene Coordinator, that a removal action would have the following characteristics:

- Where surface contamination (top 4 inches of soil) was at or above the EPA action level of 1,000 parts per trillion (ppt) for concentrations of dioxins and furans (calculated from World Health Organization 1998 Toxic Equivalence Factors for congeners of polychlorinated dibenzo-p-dioxins and furans), an 18 inch excavation and soil removal would be done.
- Confirmatory samples would be taken vertically and horizontally. If there was still contamination at depth, this would not be removed, but it would be noted and marked. Further, any soil contaminated above the action level at the surface would be removed, and removal would continue horizontally until surface soil samples did not reveal any contamination above the action level.

This plan was not perfect, even for removal of very high levels of surface contamination because the assessment of soils contaminated above the action level was to be based on composite samples taken at large intervals. Thus, there could still be "hot spots" masked by averaging. However, the plan did ensure that some genuine cleanup occurred that would not interfere with any future remedial actions that will be done following health risk assessment and ecological risk assessment activities. The Minnesota Department of Health (MDH) has participated in several conference calls with EPA, to plan risk assessment activities.

During the conference call of October 20, 2003 between EPA and International Paper (IP), it was apparent that even the minimal steps of a removal action might be in jeopardy. In particular, IP proposed an "excavation" of 4 inches of soil, to be filled in with clean soil. Soil removal at this depth will not protect gardeners, children digging, people playing sports, or doing any number of ordinary activities. It will not prevent wind erosion from uncovering more contaminated soil. It is not protective of public health. IP also said that they would not take confirmatory samples, and that this removal would be the full extent to which they would address these areas: i.e. there would be no further remedial action. When it was pointed out that a remedial action might still be

needed, IP then proposed that they would remove 4 inches, and not put clean soil on top. However, this could leave exposed soil contaminated above the action level in the next 4 inches (because the next soil samples were taken at a 4-12 inch depth, so the amount in the following 4 inches is unknown). IP reluctantly agreed to consider putting a "snow fence" around the "excavated" areas.

As you know, it is the position of MDH that any accessible soil in the area of this site, which is in a residential area, be rendered inaccessible or removed if it is above 50 ppt. MDH has made this recommendation before (*Public Health Assessment for Joslyn Manufacturing and Supply Company,* 2002). This is an interim health-based number, to protect against cancer and non-cancer effects from exposures to dioxins. A remedial action based on a human health risk assessment could result in an even lower criterion. The EPA action level of 1,000 ppt is not a health-based number.

MDH is especially concerned about on-going exposures of children in the immediate area of contamination. MDH and the Leech Lake Band of Ojibwe (LLBO) made a recommendation for soil cleanup for soils above 50 ppt in a *Health Consultation* (August 28, 2003) done under cooperative agreement with the U.S. Agency for Toxic Substances and Disease Registry (ATSDR). This document is open for public comment, and MDH intends to meet with the public in Cass Lake on October 28, 2003 to discuss health concerns about contaminated soils. Most urgently, MDH intends to repeat the recommendation, first made in a *Health Consultation* in 1993, repeated in a *Health Consultation* of 1995, and repeated again in the most recent *Health Consultation*, that the most contaminated areas of the site be fenced, so that access is immediately restricted.

The IP proposal is unacceptable. If it is implemented, it could leave the site in worse condition. This site has been in need of work for a decade. EPA needs to address it by removing the worst areas of contamination as soon as all validated data can be reviewed by concerned agencies (MDH has not yet seen the data actually discussed in the conference call). If it is too late to implement a good removal action this year, we recommend that a removal take place next spring at the latest. This removal should be *at a minimum* in accordance with the plan outlined above by Sonia Vega to MDH staff. If removal is delayed until spring, a fence should be immediately constructed.

Sincerely,

Patricia A. Bloomgren

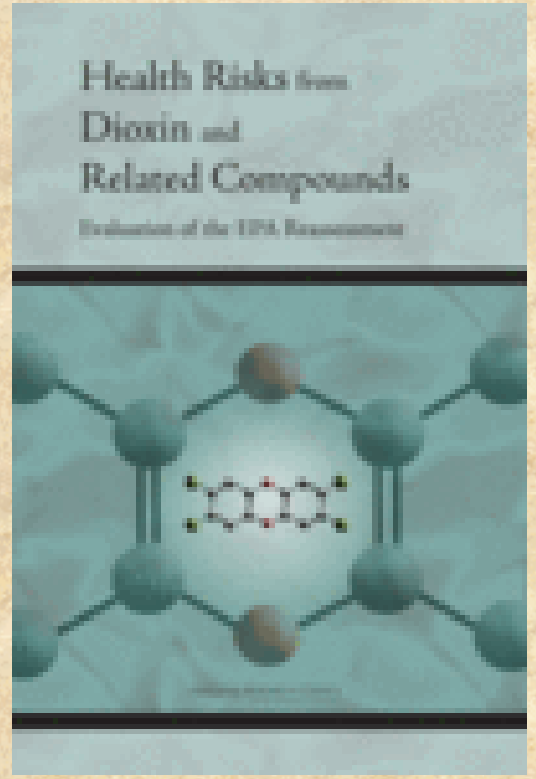
Patricia A. Bloomgren, Director
Environmental Health Division
P.O. Box 64975
St. Paul, Minnesota 55164-0975

PAB:RBM:rlk

cc: The Honorable Norm Coleman, U.S. Senate
The Honorable Mark Dayton, U.S. Senate
The Honorable James Oberstar, U.S. House of Representatives

Attachment 3
Dr. Eaton's NAS/NRC Report: Health Risks
From Dioxins and Related Compounds

NAS/NRC Report: Health Risks from Dioxin and Related Compo



The NAS and WHO on Dioxin and Dioxin Like Compounds: International Policy Implications and Potential Impacts

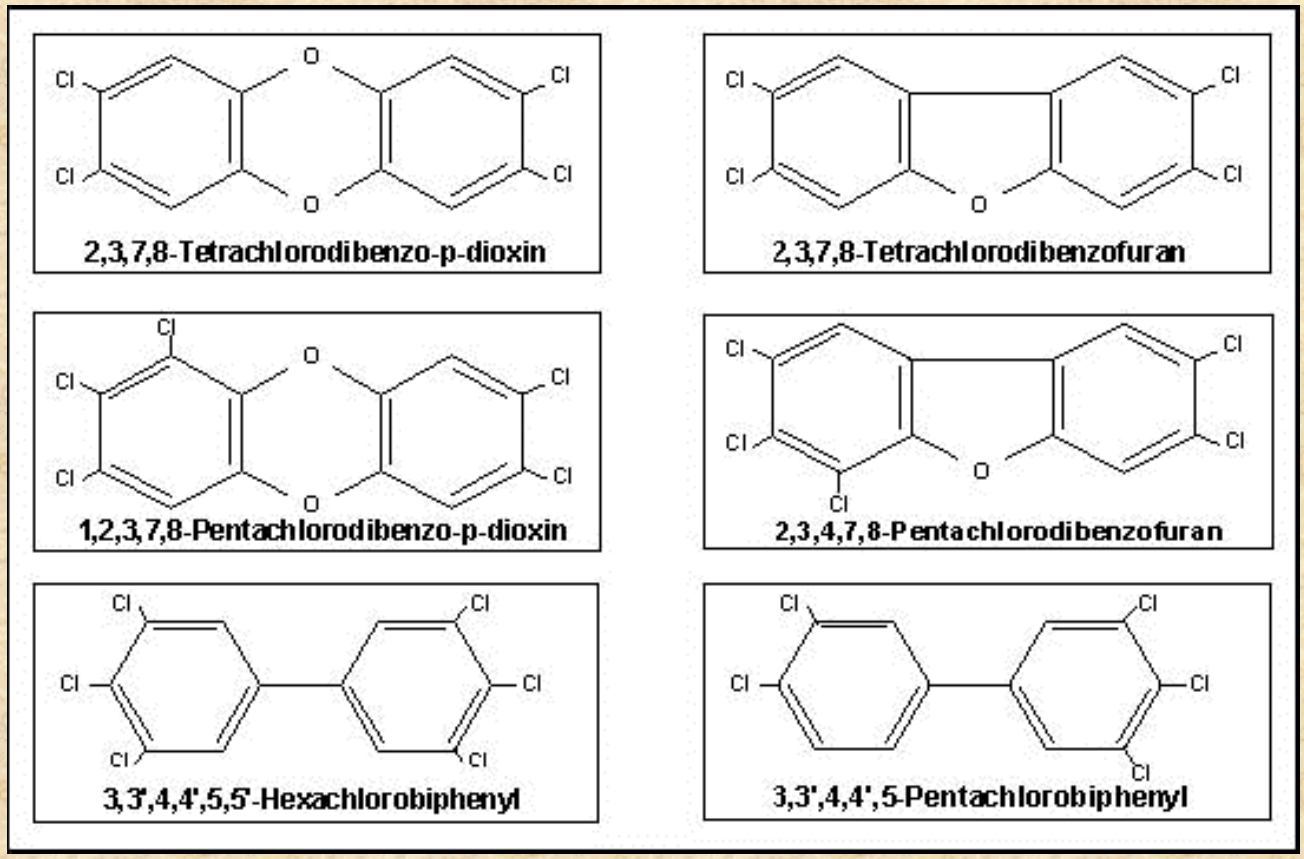
Michigan State University Superfund Program Workshop

Professor, Dept. Env. Occupational Health Sciences

Associate Vice Provost for Research
University of Washington

Dioxins, Dibenzofurans and PCBs

- Chlorinated Dioxins represent a class of compounds, of which 7 are included in EPA regulations (Contaminants – no commercial use)
- Chlorinated dibenzofurans include 10 congeners (formed from PCBs)
- Certain ‘planer’ PCBs also have ‘dioxin-like’ activity, and are included.



Toxicology of ‘Dioxin’ in 1 Minute

- Very toxic, both acute and chronic
  - LD50 0.6 ug/kg in sensitive species
  - Chronic – birth defects, immunotoxicity, cancer, chloracne, reproductive effects, liver, CNS
  - Large species differences
- Mechanism of all (or nearly all) toxic effects is by binding to the Ah Receptor
  - Transcriptional activation of numerous genes, especially CYP1A1
  - Toxic effects are result of ‘downstream’ events that follow Ah Receptor activation
- Very fat soluble, resistant to degradation
  - Persistent in the environment
  - Bioaccumulate
  - Long biological half life (about 6-7 yrs in humans)

Known Effects of TCDD in Humans

Before Dioxin poisoning

After Dioxin poisoning

Yuschenko's blood TCDD concentration was ~ 100,000 pg / g lipid

Known Effects of DLCs in Humans

- Yusho and Yu-Cheng Disease in Japan
  - Massive PCB/PCDF exposures via diet
- Michigan nursing mothers exposed to PCBs via fish consumption
- Dutch cohort of off-spring of moderately exposed mothers (DLCs, mostly PCBs)
  - Developmental abnormalities following in utero exposures, mostly neurobehavioral and cognitive deficits
  - Some evidence of immune system dysfunction
  - Some evidence of hormonal/endocrine dysfunction
- Occupational exposures – possible increase in cancers

Dioxins, Diobenzofurans & PCBs Toxic Equivalence Factors (TEFs)

Table 1-3. The toxic equivalency factor (TEF) scheme for TEQ_{DFP}-WHO_{98}[a]

Dioxin congener	TEF	Furan congener	TEF	Dioxin-like PCB	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1	PCB-77	0.0001
1,2,3,7,8-PeCDD	1.0	1,2,3,7,8-PeCDF	0.05	PCB-81	0.0001
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5	PCB-126	0.1
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1	PCB-169	0.01
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1	PCB-105	0.0001
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1	PCB-118	0.0001
1,2,3,4,6,7,8,9-OCDD	0.0001	2,3,4,6,7,8-HxCDF	0.1	PCB-123	0.0001
		1,2,3,4,6,7,8-HpCDF	0.01	PCB-156	0.0005
		1,2,3,4,7,8,9-HpCDF	0.01	PCB-157	0.0005
		1,2,3,4,6,7,8,9-OCDF	0.0001	PCB-167	0.00001
				PCB-114	0.0005
				PCB-189	0.0001

History – EPA Dioxin Risk As

- 1985 – Completed first risk assessment of Dioxi
  - Classified as potent, 'likely' human carcinoge
  - linear extrapolation, mg/kg-d dose metric
  - Controversial assumptions
- 1991 – EPA announces that it will Reassess Dic
- 1994 – First draft of Reassessment released
  - Basically supported findings of 1985 assessm
  - Used body burden as dose metric
  - Extensive peer review and public comments raised concerns about models and assumptions
- 2000 –Revision of 1994 Reassessment released
  - Additional Peer review and SAB comments
  - Questions about linear model for cancer
- 2003 – Revised 'Near Final' Reassessment
  - Requested the National Academies to do revi
- 2004 – NAS/NRC appoints panel, begins review
- 2006 – NAS/NRC report released (July)

Why is this importa
Policy implication

- Many industries, (pulp and paper, chem
manufacturers, incinerators, etc), have
that are regulated
  - Emissions standards will be based on ris
- Many state and federal (Superfund) hazardous was
sites contain dioxins/DLCs
  - clean-up standards will be based on risk
  - State agencies can set own standards (if stricter than fe
- Draft Reassessment suggested that there was pote
unacceptable cancer risks at current background le
  - Implications for regulation of foods, especially meat and
- Some regulations have been 'on hold' pending
acceptance of a final EPA Reassessment

The NAS/NRC Process
Selecting the Committee

- Committee of ‘highly respected’ scientists, with all relevant areas of expertise represented
  - Not necessarily ‘experts’ on dioxin, but have high level of credibility in their discipline
- Full disclosure of potential conflicts and biases
- Not involved in preparation or review of the EPA Reassessment
- Committee selected by the NAS leadership, following detailed ‘vetting’ of information on nominees
- Tentative Committee becomes ‘final’ committee after 1st meeting, when bias and conflict of interest are discussed

End Result – Committee of 18

- Dave Eaton, PhD, UW (Chair)
- Dennis Bier, MD, Baylor
- Joshua Cohen, PhD, Harvard (now at Tufts)
- Mike Dennison, PhD, UC-Davis
- Rich DiGiulio, PhD, Duke
- Norb Kaminski, PhD, Mich. St.
- Nancy Kim, PhD, NY St DoH
- Djien Liem, PhD, European Food Safety Authority, Italy
- Tom McKone, PhD, UC-B
- Malcolm Pike, MD, USC
- Alvaro Puga, PhD, U Cinn.
- Andy Renwick, PhD, Univ. Southampton, UK
- David Savitz, PhD, UNC (now at Mt. Sinai)
- Allen Silverstone, PhD, SUNY-Upstate (Syracuse)
- Paul Terranova, MD, KUMC
- Kim Thompson, PhD, Harvard (now at MIT)
- Gary Williams, MD, NYMC
- Yilang Zhu, PhD, U. S. Florida

Members highlighted in blue have spent much of their careers on dioxin toxicology

Committee Charge

The NAS/NRC will convene an expert committee that will review EPA's 2003 draft Reassessment….to assess whether:

- Risk estimates are scientifically robust
- There is a clear delineation of all substantial uncertainties and variability
- To the extent possible, focus on:
  - Modeling assumptions (shape of D-R curve, points of departure, dose ranges for likely human health outcomes)
  - EPA's quantitative uncertainty analysis
  - EPA's selection of studies as a basis for its assessments
- Also address:
  - Scientific evidence classifying TCDD as a human carcinogen
  - Validity of the non-threshold, linear D-R model and slope factors
  - Usefulness of TEF/TEQ approach

Other Conditions / Limitations

- Complete the review in 18 months
  - including peer review, revisions, and final
- Solicit public input prior to writing repo
- Strive for a ‘Consensus’ report
- Have no more than 5-6 meetings
- Draft report subject to extensive peer review
- Final report must include consideration of <u>all</u> peer review comments
- We focused our on review Part III of th
  - “Integrated Summary and Risk Characteriz
  - ~200 page summary of the several thousa
- Considered ‘new information’ only if it assumptions, and likely to change the RA

Process

- 2 meetings with i tations
  - Heard from 16 c d parties'
  - Received piles of solicited and unsolicited informat
- Organized the report to include 8 chapters:
  1) Introduction
  2) General Considerations of Uncertainty and Variability, Selection of Dose Metric, and Dose-Response Modeling
  3) Toxic Equivalency Factors
  4) Exposure Assessment
  5) Cancer
  6) Non-Cancer Endpoints (Immune, ent, Other)
  7) Risk Characterization
  8) Conclusions and Recommendatic
- Chapter review assignments made by Chair, based on areas of expertise – 3-4 members per topic
- 2 meetings to discuss recommendations
- 1 meeting to finalize report conclusions and consensus
- Most of the real work was done by e-mail

Process (cont)

- Consensus draft report completed in December, 2005
- Edited by staff then sent to 15 different peer reviewers
- 3 months later, received ~120 pages of comments
- Made numerous changes (requiring approval of all committee members) and submitted revised to NAS/NRC Study Monitor
  - along with detailed list of how document was changed in response to comment, and if not, why not
- After approval of Study Monitory, Final draft report sent to NRC staff for editing and printing
- Congressional Briefings and Press Conference held on day before report was released (July 11, 2006).

Key Findings of The Committee

- “3 areas that require substantial improvement in describing the scientific basis for EPA’s dioxin risk assessment”
  - Justification of approaches to D-R modeling
  - Transparency and clarity in selection of key data sets
  - Transparency, thoroughness and clarity in quantitative uncertainty analysis
- Classification of TCDD as known vs. likely human carcinogen
  - Use the new definitions in 2005 CAG
- TEFs continue to be best approach for assessing mixtures
- Encouraged EPA to calculate RfD and MOE scenarios

Key issue – Qualitative Assessment of TCDD carcinogenicity to humans

- Seems to be a ‘big deal’ to lots of people
- Committee felt that it really was not important, as TCDD will (and should) be regulated as if it is carcinogenic to humans regardless of what label it is given
- Better off spending time on more critical uncertainties that will affect the quantitative risk estimations
- Guidelines and definitions changed in 2005 – EPA should use new guidelines, then justify their decision
- Committee was ‘split’ on whether the available data met the criteria of the new guidelines
  - Full agreement that it was at least likely to be carcinogenic in humans
  - Other DLC congeners ‘Likely’ to be carcinogenic to humans

"Carcinogenic to Humans"
EPA Carcinogen Assessment Guidelines 2005

This descriptor indicates strong evidence of human carcinogenicity.

This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.

Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when all of the following conditions are met:

(a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, **and**

(b) There is extensive evidence of carcinogenicity in animals, **and**

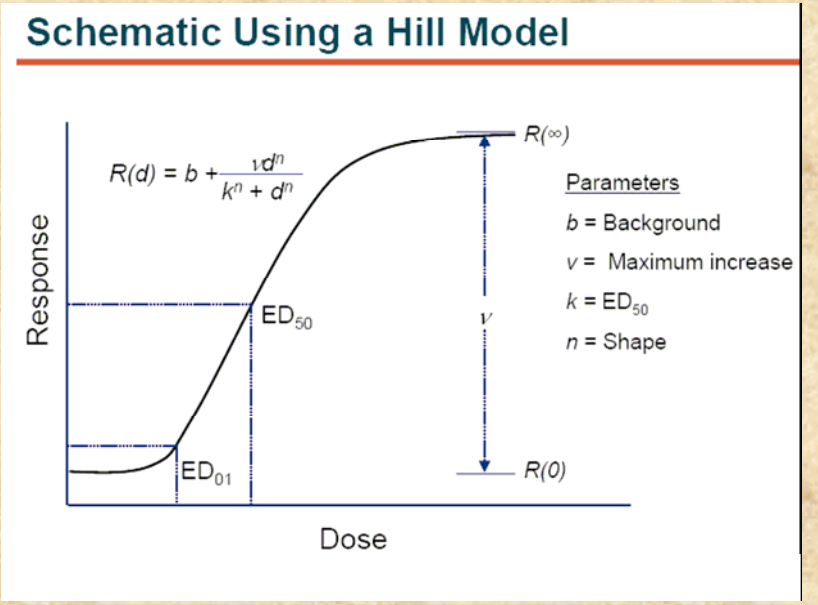
(c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, **and**

(d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information.

Epidemiological Evidence

- Four occupational cohorts with substantial TCDD exposure
  - Ott & Zober, 1996 – 1953 accidental exposure (N=243, 13 cancer deaths)
  - Becher et al 1998 – Pesticide production cohort (N=1189; 124 Ca deaths)
  - Fingerhut et al (’90, 91) – 12 manufacturing facilities (N=5172; 377 deaths)
  - Steenland et al (2001) – update on Fingerhut cohort (N=3538; 256 deaths)
  - De Mesquita et al (1993) – Phenoxy production (N=2310, 31 cancer deaths)
- Most, but not all, found significant increase in all cancers, but no consistent increase in any specific tumor type
- Committee conclusions:
  - Overall, the committee concurs with the value of conducting analyses of total cancers given the potential for dioxin to affect multiple types of cancer
  - “It was the Committee’s impression that EPA’s narrative tended to focus on positive findings without fully considering the strengths and limitations of both positive and negative findings.”

Key Issue – Shape of the D-R Curve



- Mode of action – Receptor-mediated for all end points
- Non-genotoxic
- Evidence of tumor promotion
- Binding to Ah receptor is necessary, but not sufficient, to cause cancer
- Existing animal and human epi data provide little guidance as to the shape of the D-R at response levels below 5-10%

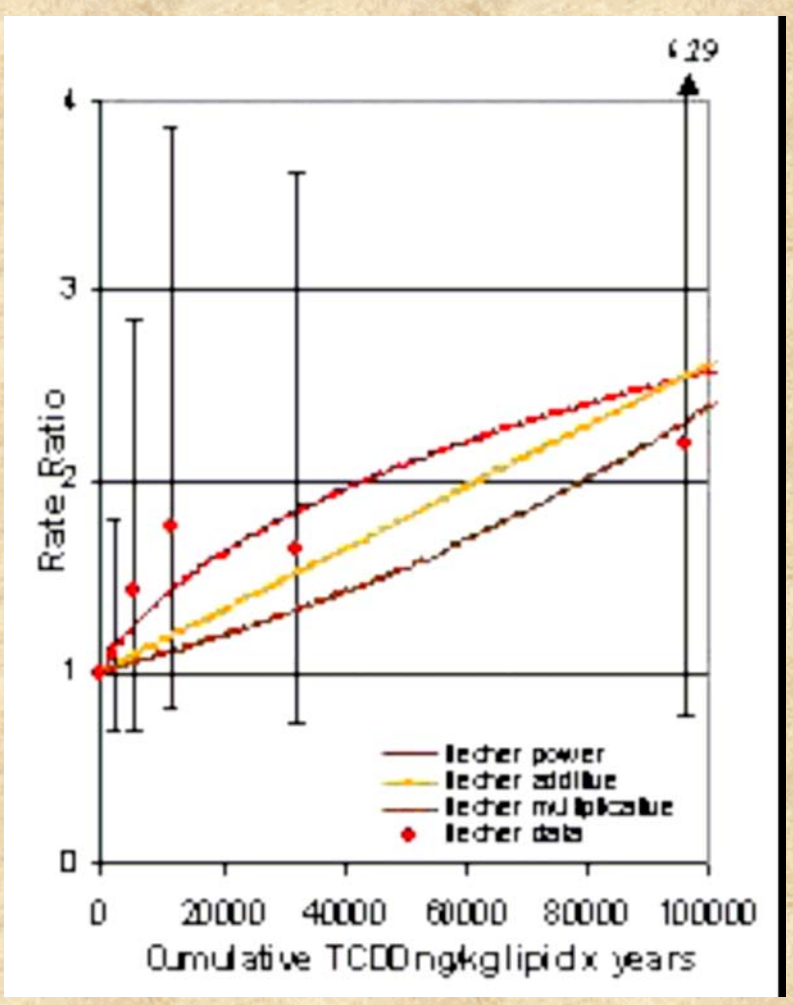
Rationale for EPA's Choice of Linear, non-threshold model

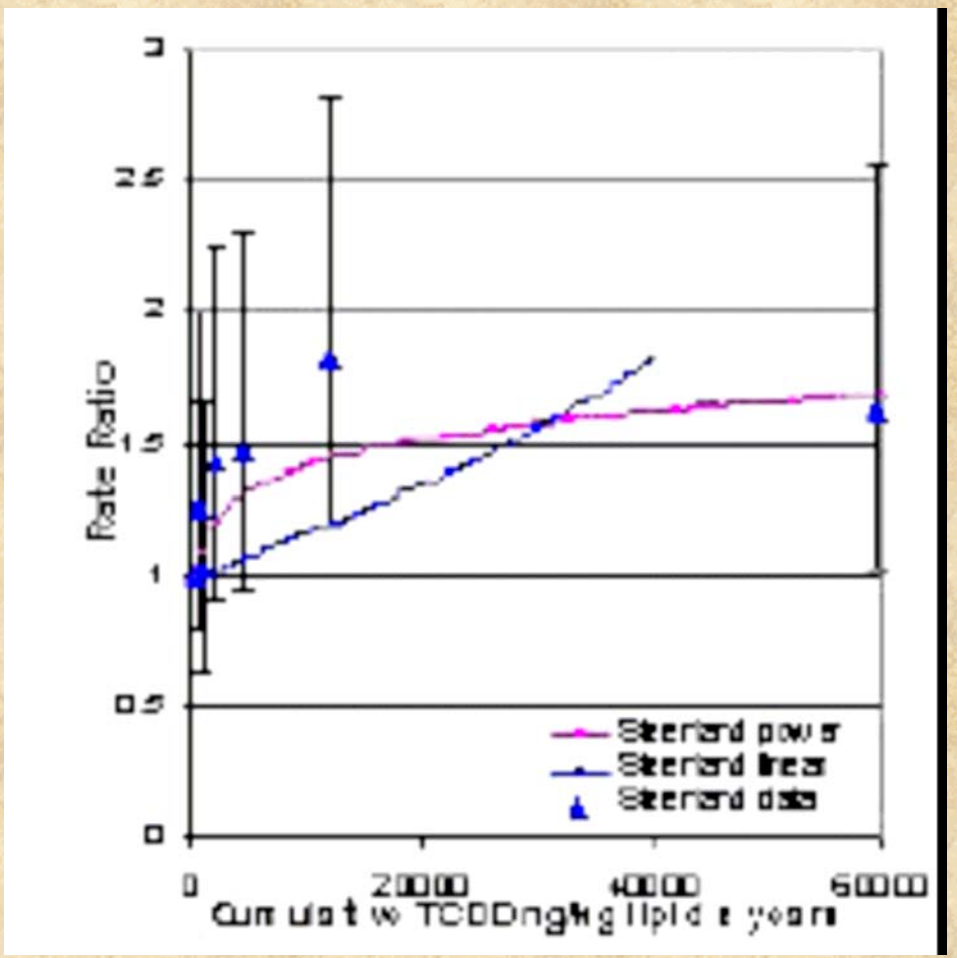
- *"At this time, the knowledge of the mechanism of action of dioxin, receptor theory, and the available dose-response data do not firmly establish a scientific basis for replacing a linear procedure for estimating cancer potency."*
- *"The linear default is selected on the basis of the agent's mode of action when the linear model cannot be rejected and there is insufficient evidence to support an assumption of non-linearity"*
- Committee disagreed with using the 'default' assumption, given the enormous amount of data on dioxin mode of action, and noted that EPA had used non-linear modeling for other receptor-mediated carcinogens (thyroid carcinogens, estrogens, etc.)
- Recommended that they do BOTH, to illustrate the importance of this assumption
- If they choose to use the linear estimates out of 'precaution', that would be a policy decision, with the implications clearly described

Key Issue – Point of Departure

- EPA used a POD of 1%: *"The curve-fitting procedure is used to determine a POD, generally at the 10% response level, but when more sensitive data are available, a lower point for linear extrapolation can be used to improve the assessment (e.g., 1% response for dioxin, ED01).*
- They calculated 1% PODs from the epidemiology data, using various models
- Use of ED05 would greatly expand the Confidence Limits around the central estimate (from which the Slope factors are derived)
- "It is evident that the choice of POD can have a substantial impact on the uncertainty of the final risk estimate – importance of this assumption is not readily evident in the Reassessment""

EPA Modeling of Cancer Data for ED01





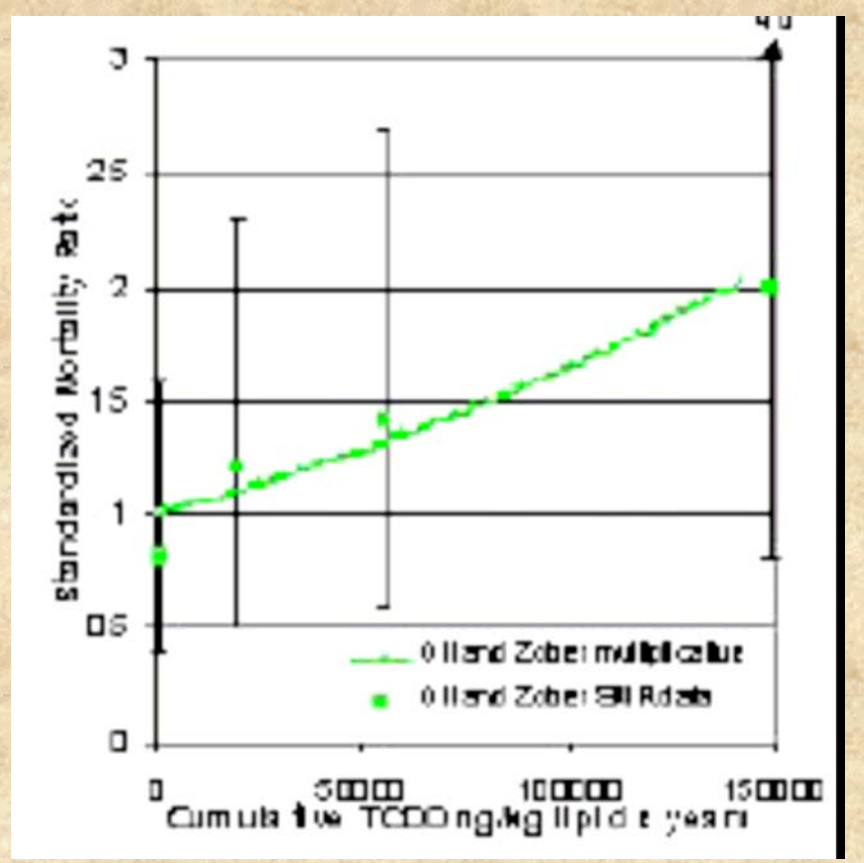
Hamburg Cohort

Mean Serum TCDD: 507 (2 – 6397 ppt)

NIOSH cohort

Mean Serum TCDD: 2000 (2 – 32000 ppt)

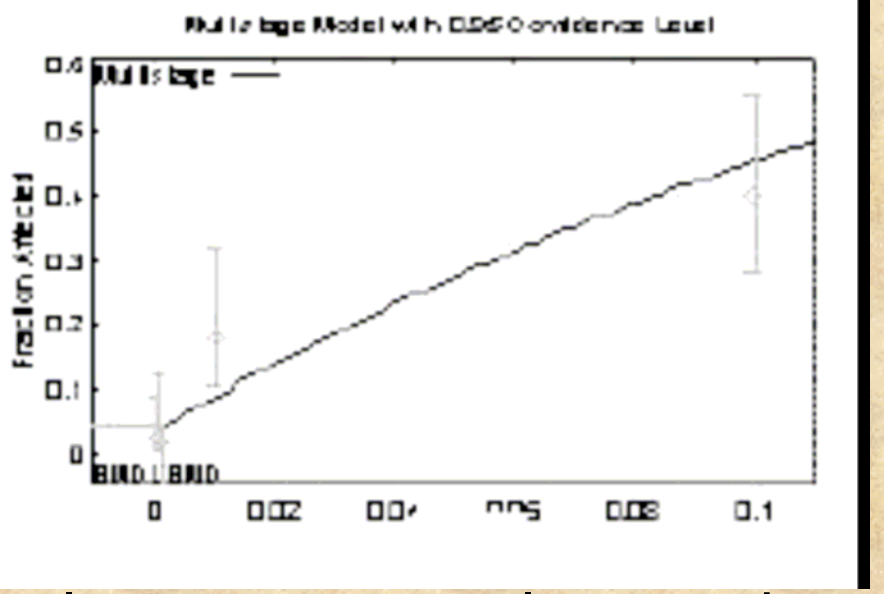
EPA Modeling of Cancer Data for ED01



BASF cohort

Mean Serum TCDD: 1008 (20 – 13360 ppt)

Exposure groups	Central estimate of range (ng/kg fat x years)[a]	All cancer deaths observed (latency)
0	0	2/86 Tumors
0.001	540	1/50
0.01	1700	9/50
0.1	8100	18/45
µg/kg/day	ng/kg lipid, not AUC	



Male Sprague-Dawley Rat data

Cancer Slope Factors Derived from ED01 modeling

Table 5-3. All cancer risk in humans through age 75[a]

Study	Model and Sex	ED_{01}	95% CI (lower, upper)	Unit excess risk for 1 ppt body burden above background
Steenland et al. (2001)	power male	1.38	0.71, 8.95	0.0079 (0.0027, 0.0132)
	power female	1.84	0.92, 14.9	0.0064 (0.0022, 0.0107)
	piecewise linear male	18.6	11.5, 48.3	0.00052 (0.00020, 0.00084)
	piecewise linear female	23.1	14.3, 59.8	0.00042 (0.00016, 0.00067)
Becher et al. (1998)	power-male	5.971		0.0018
	power-female	7.58		0.0014
	additive-male	18.22		0.00055
	additive-female	22.75		0.00044
	multiplicative-male	32.16		0.0003
	multiplicative-female	39.82		0.00024
Ott and Zober (1996)	multiplicative-male	50.9	25.0, ∞	0.00019 (0, 0.00039)
	multiplicative-female	62.1	30.5, ∞	0.00015 (0, 0.00032)

[a] Units are constant body burden in ng/kg not adjusted for lipid: see Part III, Chapter 8, Table 8-2, for details.

EPA Conclusions for Cancer Slope Factors

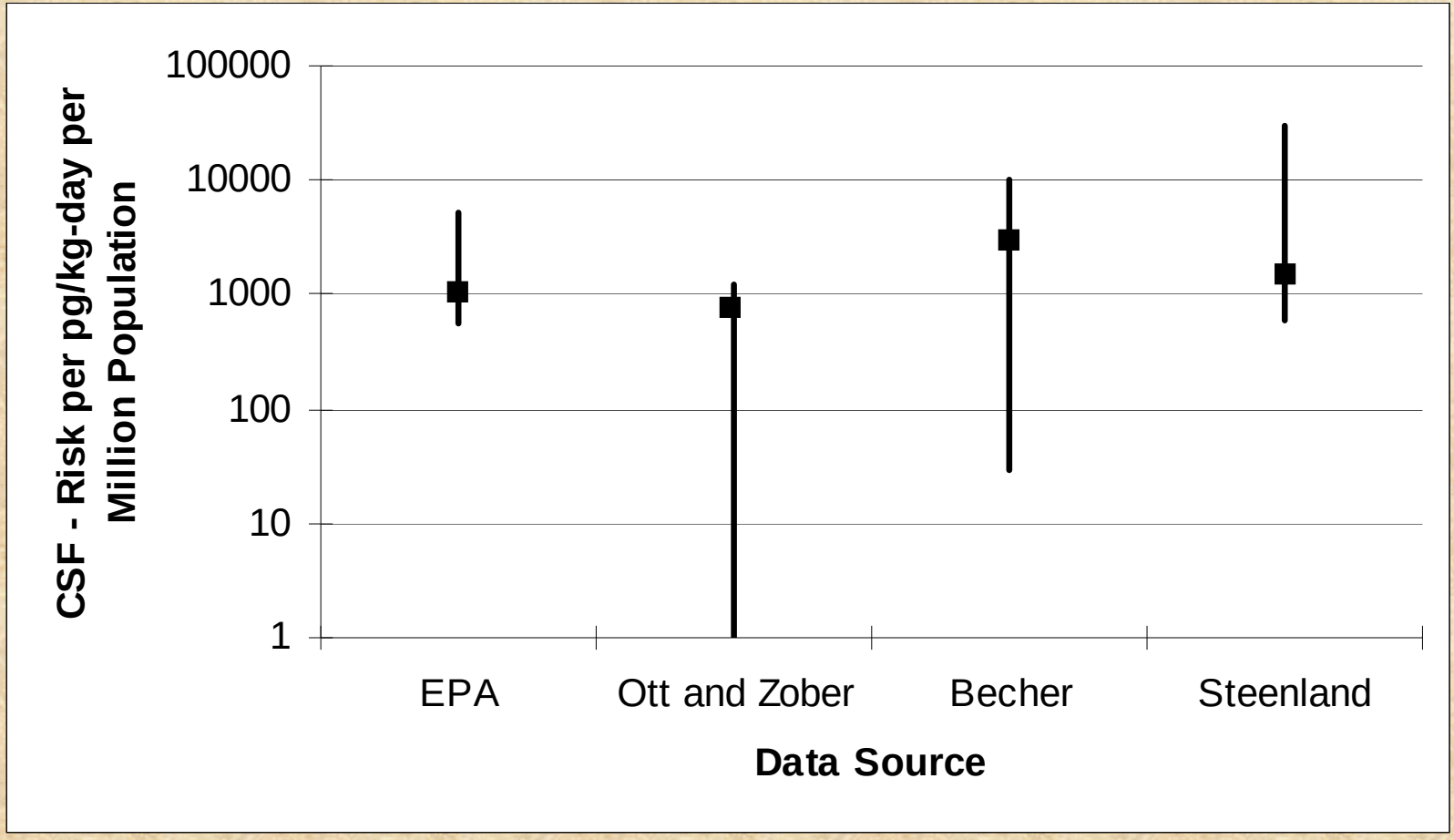
Table 5-4. Summary of all site cancer ED_{01} and slope factor calculations

Study	ED_{01} (LED_{01}) (ng/kg)	Cancer slope factor for 1 pg/kg/day above background[a] (UCL)
Hamburg cohort, Becher et al. (1998), power	6	5.1 E-3
Hamburg cohort, Becher et al. (1998), additive	18.2	1.6 E-3
Hamburg cohort, Becher et al. (1998), multiplicative	32.2	0.89 E-3
NIOSH cohort, Steenland et al. (2001), piecewise linear[b]	18.6 (11.5)	1.5 E-3 (2.5 E-3)
BASF cohort, from Ott and Zober (1996), multiplicative	50.9 (25.0)	0.57 E-3 (1.2 E-3)
Sprague-Dawley rats, Kociba et al.(1978); Goodman and Sauer (1992), pathology	31.9 (22)[c] BMD dose 38 (27.5) BMD adipose	0.97 E-3 (1.4 E-3) 0.8 E-3 (1.1 E-3)

Main concern of Committee

- Significance of ED01 vs. ED05 for POD
- Alternative, biologically plausible, dose-response functions
- Final cancer slope factor estimates from Epi studies ranged from 0.9×10^{-3} to 5.1×10^{-3} (6-fold) and compared with two estimates from rats data of 0.8×10^{-3} and 0.97×10^{-3}. (all within a factor of 10).
- Committee felt that the range of uncertainty is greater than indicated in Reassessment

NRC Report
Range of Plausible CSF Values –
Consideration of Parameter Confidence Intervals Only



Key Issue – Dose Metric

- EPA used ‘body burden’ rather than daily intake rate (pg/kg/day)
- Makes a very substantial difference (~280-fold) in cancer risk estimates from animal studies because of species differences in half-lives (~100-fold) and body fat composition, and thus the daily dose that yields a particular dioxin body burden at steady state
- Committee agreed with EPA that body burden, although not perfect, is the best dose metric to use for TCDD and DLCs, given their long half-lives and bioaccumulation in adipose tissue.

Key Issue – Use of TEF/TEQ

- Use new TEFs from WHO
- Encourage development of stronger scientific basis for individual congener TEFs, esp. those that are ‘drivers’
- Background levels of dioxins in environment are declining- are body burdens also?
- Most of the body burden is a result of a few congeners, and little or no TCDD

- EPA Reassessment used a ‘peak’ TEQ value of 55 pg/g lipid (30 – 70 CLs) as median US Background, and 5.2 +/- 1.3 pg/g lipid for TCDD -- from 1990’s

Table 93. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) (lipid adjusted)

Geometric mean and selected percentiles of serum concentrations (in pg/g of lipid or parts per trillion on a lipid-weight basis) for the U.S. population, National Health and Nutrition Examination Survey (1999-2000, aged 12 years and older; 2001-2002, aged 20 years and older).

	Survey years	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Total, age 20 and older	99-00	*	< LOD	< LOD	< LOD	< LOD	1240
	01-02	*	< LOD	< LOD	< LOD	< LOD	1228
Age group							
12-19 years	99-00	*	< LOD	< LOD	< LOD	< LOD	658
	01-02	†	†	†	†	†	†
20 years and older	99-00	*	< LOD	< LOD	< LOD	< LOD	1240
	01-02	*	< LOD	< LOD	< LOD	< LOD	1228
Gender (20 years and older)							
Males	99-00	*	< LOD	< LOD	< LOD	< LOD	572
	01-02	*	< LOD	< LOD	< LOD	< LOD	559
Females	99-00	*	< LOD	< LOD	< LOD	< LOD	668
	01-02	*	< LOD	< LOD	< LOD	6.40 (<LOD-9.10)	669
Race/ethnicity (20 years and older)							
Mexican Americans	99-00	*	< LOD	< LOD	< LOD	< LOD	336
	01-02	*	< LOD	< LOD	< LOD	< LOD	262
Non-Hispanic blacks	99-00	*	< LOD	< LOD	< LOD	< LOD	222
	01-02	*	< LOD	< LOD	< LOD	7.40 (<LOD-10.0)	217
Non-Hispanic whites	99-00	*	< LOD	< LOD	< LOD	< LOD	567
	01-02	*	< LOD	< LOD	< LOD	< LOD	665

< LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample. See Appendix A for LODs.

* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

† Data not collected for this age group for these years.

Table 87. 1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin (HxCDD) (lipid adjusted)

Geometric mean and selected percentiles of serum concentrations (in pg/g of lipid or parts per trillion on a lipid-weight basis) for the U.S. population, National Health and Nutrition Examination Survey (1999-2000, aged 12 years and older; 2001-2002, aged 20 years and older).

LOD = 9.1 pg/g lipid

	Survey years	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval) 50th	75th	90th	95th	Sample size
Total, age 20 and older	99-00	*	< LOD	36.1 (31.5-40.5)	62.8 (53.6-69.1)	75.6 (70.5-84.2)	1237
	01-02	34.6 (29.6-40.6)	39.2 (32.7-44.7)	60.7 (50.3-74.2)	95.2 (76.2-120)	127 (99.4-153)	1234
Age group							
12-19 years	99-00	*	< LOD	< LOD	< LOD	26.7 (20.2-29.6)	648
	01-02	†	†	†	†	†	†
20 years and older	99-00	*	< LOD	36.1 (31.5-40.5)	62.8 (53.6-69.1)	75.6 (70.5-84.2)	1237
	01-02	34.6 (29.6-40.6)	39.2 (32.7-44.7)	60.7 (50.3-74.2)	95.2 (76.2-120)	127 (99.4-153)	1234
Gender (20 years and older)							
Males	99-00	*	< LOD	34.4 (27.2-40.5)	59.2 (47.1-68.5)	73.0 (64.4-81.9)	569
	01-02	34.1 (28.3-41.1)	38.8 (31.5-44.6)	61.3 (50.0-79.5)	94.7 (70.8-131)	128 (88.5-181)	564
Females	99-00	*	< LOD	37.9 (32.5-41.6)	65.6 (55.1-70.5)	82.8 (69.3-98.9)	668
	01-02	35.1 (29.9-41.2)	40.1 (32.4-46.3)	59.8 (49.8-72.3)	97.0 (77.1-114)	126 (108-142)	670
Race/ethnicity (20 years and older)							
Mexican Americans	99-00	*	< LOD	24.2 (<LOD-32.4)	46.8 (38.1-56.1)	59.5 (52.7-67.9)	332
	01-02	18.3 (15.6-21.4)	21.2 (19.4-25.0)	31.9 (27.0-40.3)	51.5 (40.3-69.9)	67.9 (48.0-111)	260
Non-Hispanic blacks	99-00	*	< LOD	35.1 (28.4-44.9)	62.8 (48.0-79.2)	84.9 (72.2-98.1)	223
	01-02	38.9 (33.6-45.0)	40.2 (33.5-47.3)	63.2 (54.6-76.9)	93.9 (78.5-132)	133 (92.6-185)	219
Non-Hispanic whites	99-00	*	< LOD	38.2 (34.4-42.0)	64.4 (54.3-69.3)	77.7 (69.9-84.9)	567
	01-02	37.8 (31.5-45.4)	42.6 (33.9-51.1)	65.0 (52.3-82.2)	99.6 (78.4-130)	130 (103-165)	671

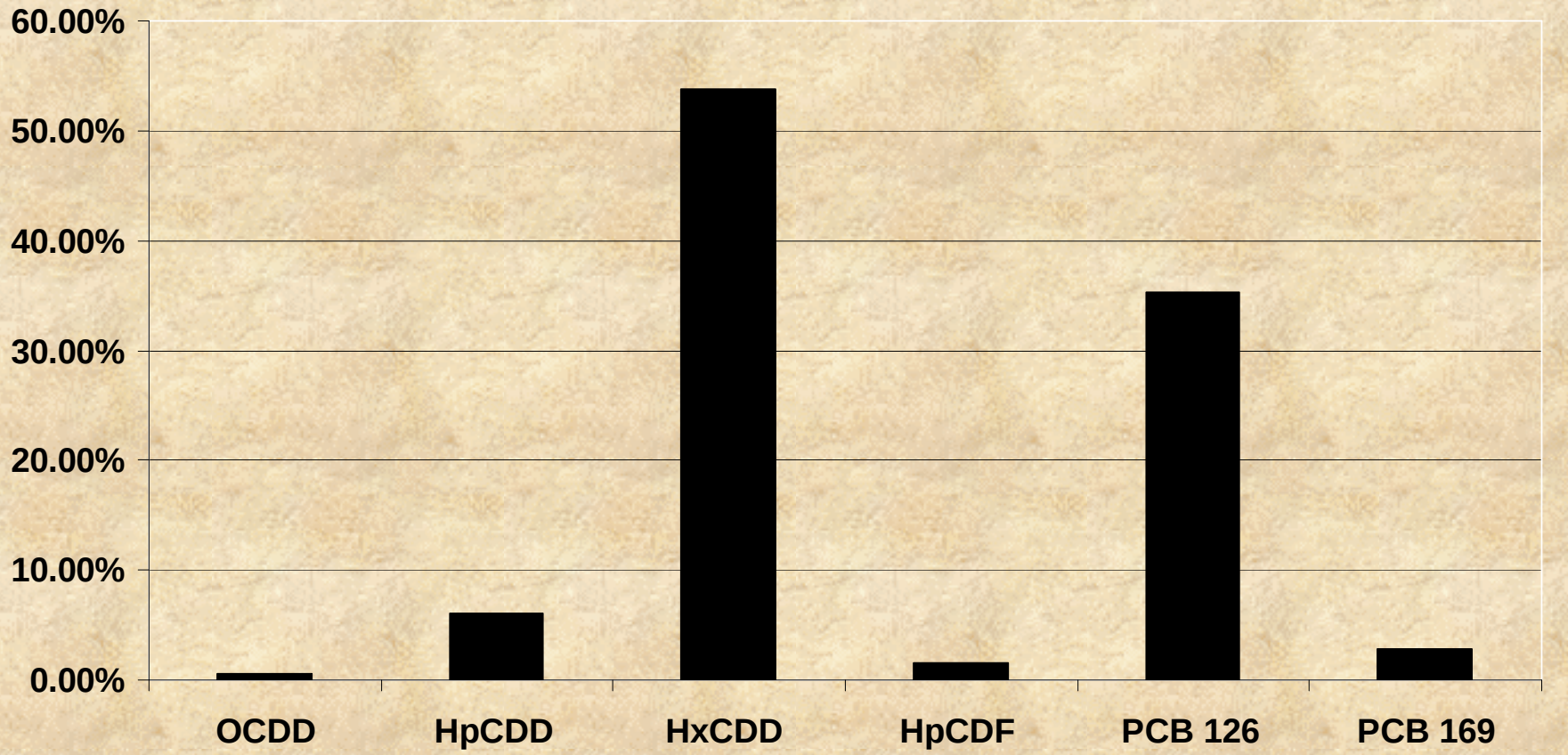
< LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample. See Appendix A for LODs.

* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

† Data not collected for this age group for these years.

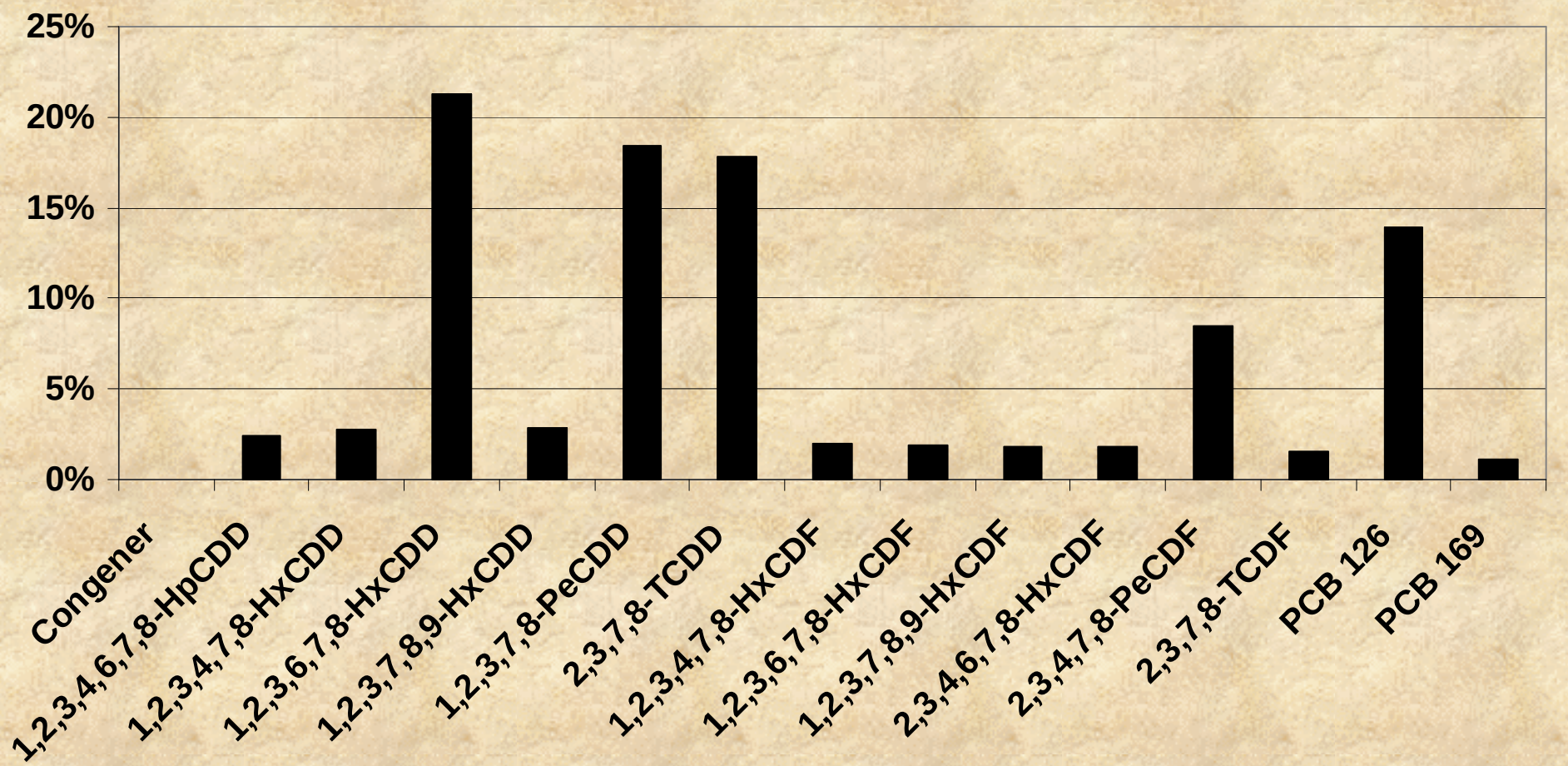
Background serum levels of Dioxin TEQs in NHANES II (US, 2001)

Assumes that non-detects are Zero
Sum of GM for all detects = 6.4 pg/g lipid



NHANES II Dioxin TEQ Data

Geometric Mean, using 0.5 x DL for non-detects
Sum of GM = 16.3 pg/gm lipid; Sum of 95% = 60.8 pg/gm lipid

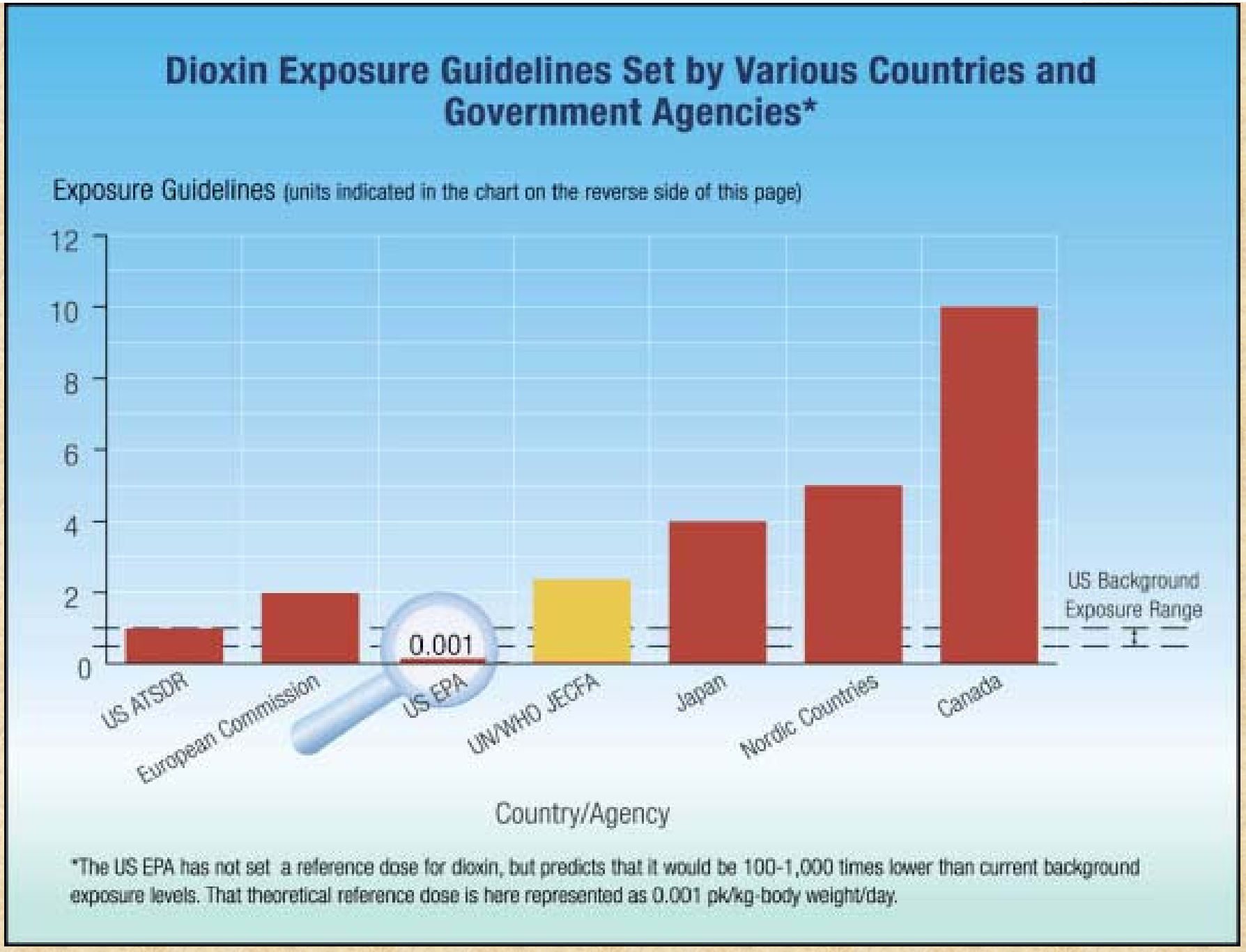


Key Issue- Calculation of RfD

- EPA chose not to calculate a Reference Dose or Margins of Exposure, primarily because their risk estimates would have resulted in low (or negative) MOEs.
- However, EPA's approach for RfD/MOE calculations use a number of uncertainty factors (such as a factor of 10 going from rodents to humans), which may not be necessary if Body Burden is used as dose metric
- WHO and many other countries utilize this approach

Bottom Line implications

- EPA's draft Reassessment arrived at a cancer slope factor of 1×10^{-3} per pg TEQ/kg/day
  - If 1 excess cancer per 100,000 was used as the 'acceptable risk' level, this would result in an 'Tolerable Daily Intake' rate of 1×10^{-5} pg TEQ/kg/d, or 0.01 pg TEQ/kg/d
  - If 1 excess cancer per 1 million was used, the TDI= 0.001 pg/kg/d
- These risk levels are based on the linear extrapolation assumption. Use of a non-linear risk estimates would use a Benchmark dose and Uncertainty factor approach



From Chlorine Chemistry Council

Next steps

- Although highly critical of a few key assumptions overall the Com done in the EP/
- "Committee rec substantial amount of effort for EPA to the changes re
- "Nevertheless, finalize the curr and concisely as possible after addres recommendations in the report"

Midland Daily News

1/04/07

Dioxin bill signed by Granholm

Legislation allowing the state to begin recalculating the dioxin cleanup standards by incorporating the recommendations made by the National Academy of Sciences was signed into law on Dec. 31, 2006.

"This legislation calls for the best available science to better protect our health and our natural resources," Moolenaar said. "The Legislature and governor have come together to support using sound science for environmental cleanup, including the work conducted by the independent National Academy of Scientists, to lead to a more productive resolution."

Attachment 4
Dr. Devito's presentation: Dose Response Relationships for Dioxins; Implications for Pubic Health

United States Environmental Protection Agency

Dose Response Relationships for Dioxins: Implications for Public Health

Michael DeVito
Chief, Pharmacokinetics Branch
USEPA

Office of Research and Development
National Health & Environmental Effects Research Laboratory

October 15, 2007

United States Environmental Protection Agency

Outline

- Dose
- Response Modeling
- Non-Cancer endpoints
- Cancer
- Summary

Dose Metrics

- **A measure of dose that incorporates physical chemical and/or biological attributes that relates exposure to a biological response. A useful metric is easy to measure and interpret**

- Exposure
  - mg/kg; mg/kg/d; ppm

- Tissue Concentration or Body Burden
  - Peak
  - Average lifetime
  - Window of Sensitivity

- Area Under the Curve (AUC)
  - Lifetime
  - Window of Sensitivity
  - Time over a set concentration

United States Environmental Protection Agency

Dose metrics used for Pharmaceuticals

- Administered Dose
- Plasma/Blood Concentrations
  - Single dose: terminal elimination phase
  - Repeated dose: Css

Blood/Plasma concentrations are related to concentration of drug at target site

United States Environmental Protection Agency

Do we need different dose metrics for environmental chemicals?

- Extrapolation
  - Across species
  - Across exposure scenarios/paradigms
  - In vitro to in vivo
- Dose Response Assessment
  - Cancer vs non-cancer
  - Adult vs developmental toxicities

United States Environmental Protection Agency

Methods for Cross-Species Dose Extrapolation in Risk Assessments

- Uncertainty Factors (10X)
  - Animal to human
  - Acute to chronic exposures
- Allometric scaling
  - Biochemical and physiological processes scale across species by functions of body mass or surface area
- “Mechanistic approaches”
  - Physiologically-based pharmacokinetic models
  - Systems Biology approach

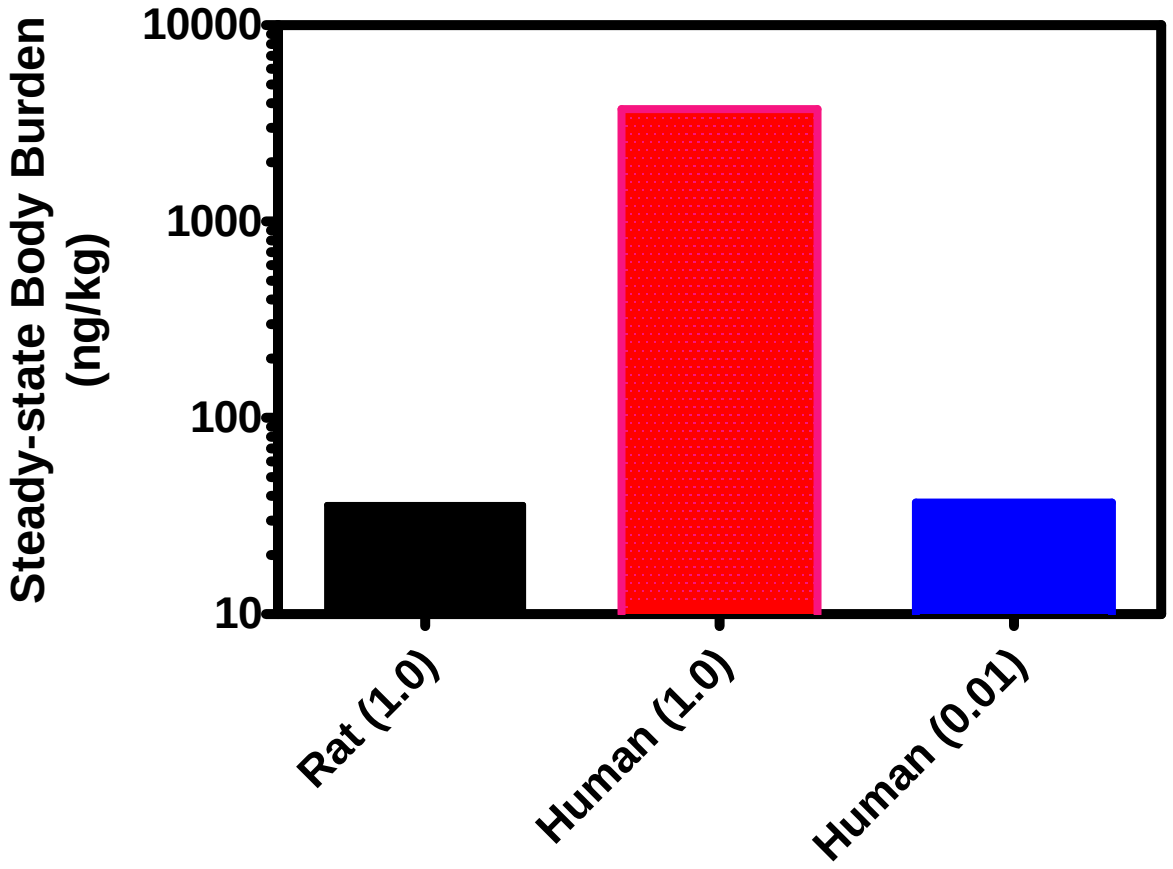
United States Environmental Protection Agency

Species Differences in Half-lives of Dioxin (TCDD)

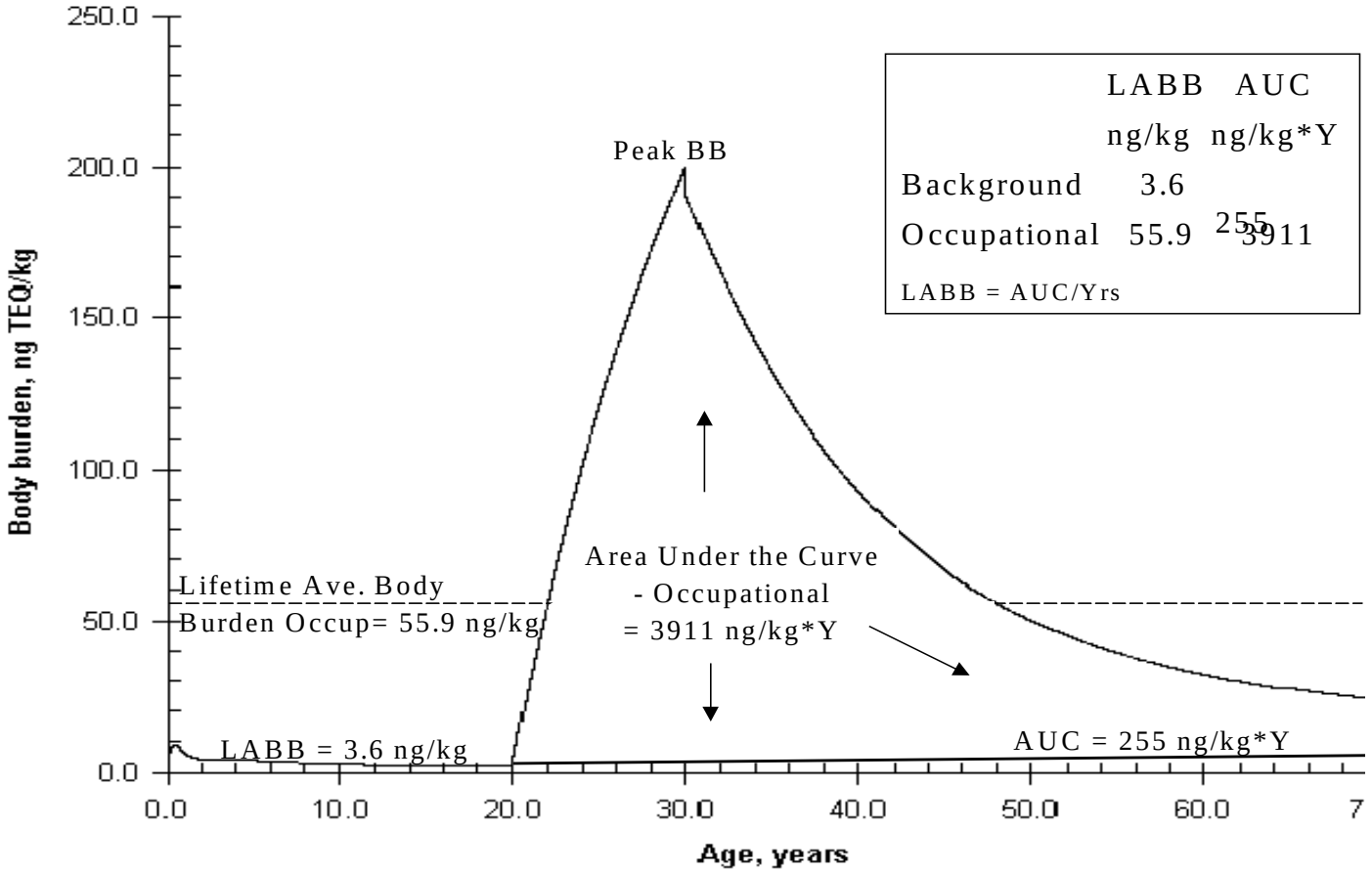
	Experimentally Estimated Half-life (days)	Allometric Scaling (body weight) of Mouse Half-life (days)
Mice	**10**	**--**
Rat	**15-25**	**18.9**
Rhesus Monkey	**400**	**39.8**
Humans	**2593**	**76.9**

United States Environmental Protection Agency

Steady-state Body burdens following 1 or 0.01 ng TCDD/kg/d exposure



Comparison of Lifetime Average Body Burden and Area under the Curve in Hypothetical Background and Occupational Scenarios



United States Environmental Protection Agency

Tissue Dose as Dose Metric for TCDD

- Based on Diliberto et al (1996 and 2001)
  - Female B6C3F1 mice exposed oral gavage
    - Single exposure 3 dose levels and 4 time points (7-35 days)
    - Repeated dose study 5d/wk for up to 17 weeks
  - dose response and time course study of disposition and enzyme induction
- Fit the Hill model to the hepatic enzyme data using either administered dose, tissue concentration, or body burden as the dose metric

United States Environmental Protection Agency

Relationship between different dose metrics and response to TCDD

Figure 1a.
Liver Concentration vs. Hepatic EROD
(Combined Acute and Subchronic Data)

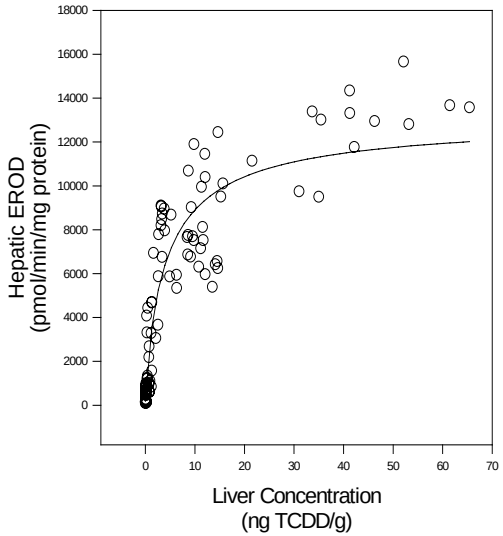


Figure 1 c.
Blood Concentration vs. Hepatic EROD
(Combined Acute and Subchronic Data)

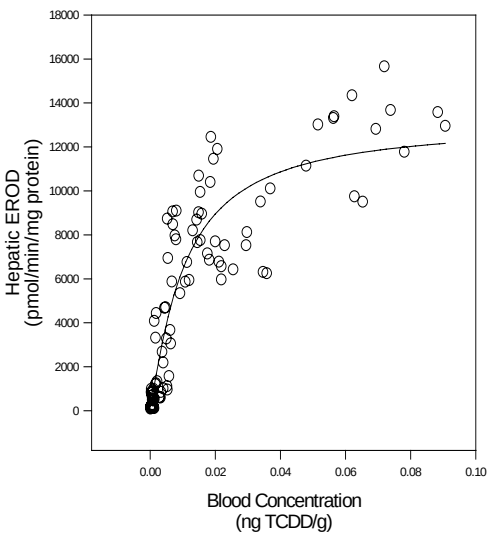
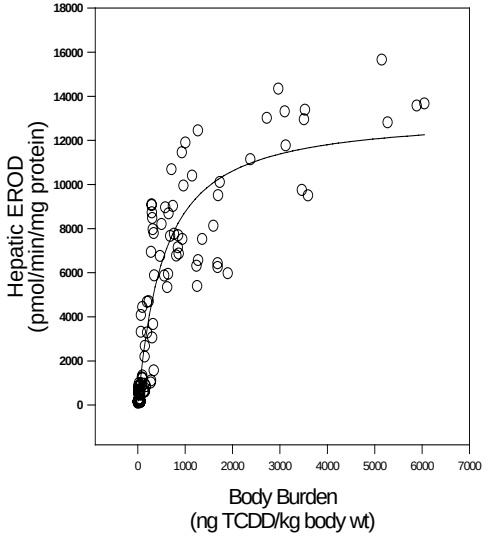


Figure 1 b.
Body Burden vs. Hepatic EROD
(Combined Acute and Subchronic Data)



Dose Metrics for Developmental Effects (Hurst et al., 1998, 2000)

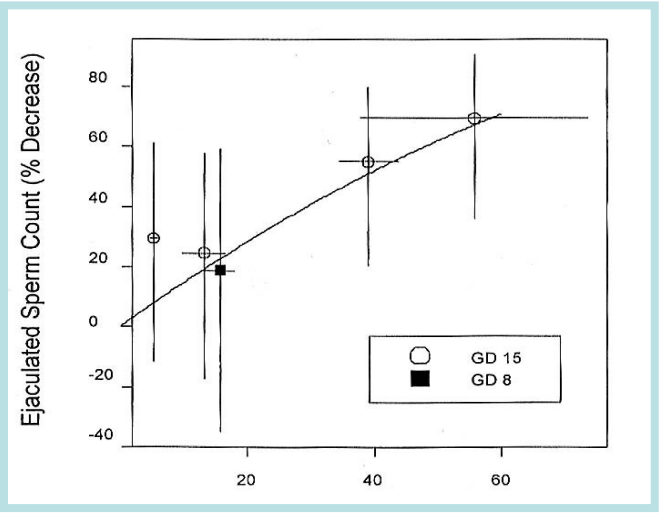


Figure 1. Percent decrease in ejaculated sperm count versus estimated mean fetal TCDD concentration on GD16.

- Tissue concentrations provide good prediction of effect.

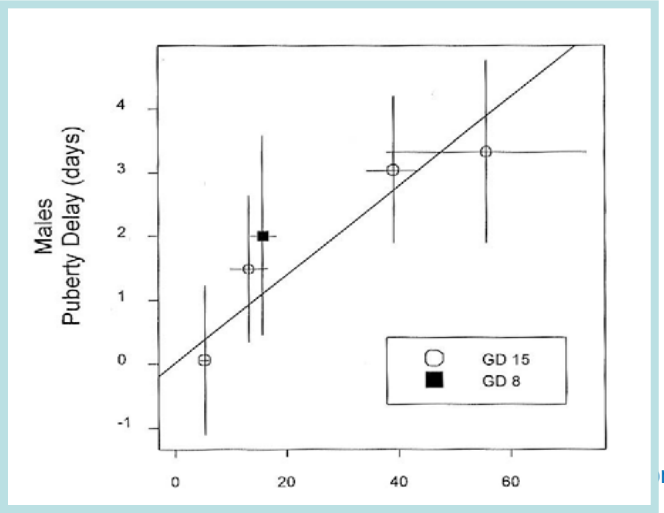


Figure 2. Puberty delay in males versus estimated mean fetal concentration on GD16.

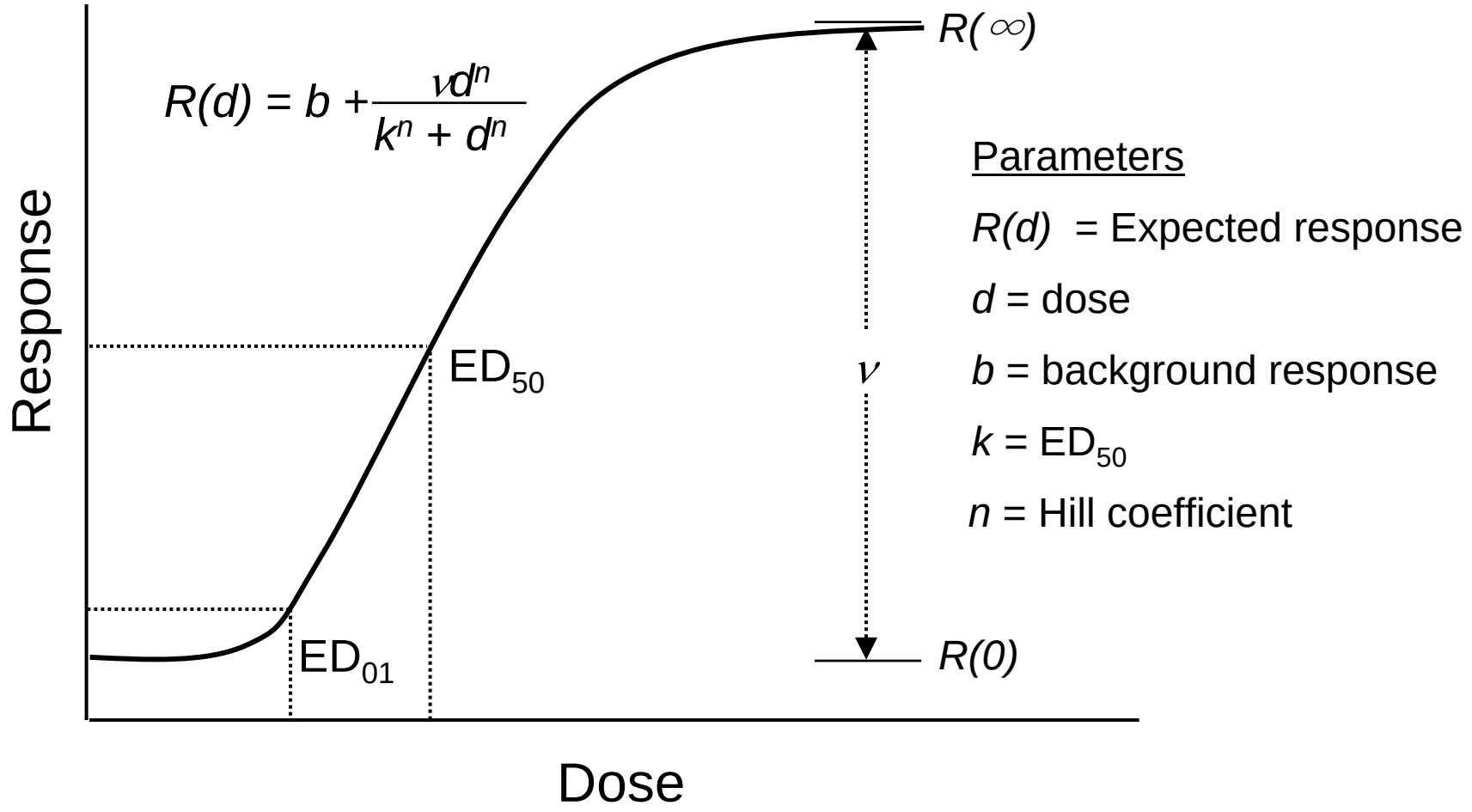
- Tissue concentrations provide good prediction of effect.

United States Environmental Protection Agency

Benchmark Dose Approach

- Statistically-derived dose that gives a prespecified increase in response or “risk”
- All dose-response data used
- Proposed as an alternative to the use of No-Observed-Adverse-Effect-Level (NOAEL) for estimating a point of departure.

Hill Model


$R(d) = b + \frac{\nu d^n}{k^n + d^n}$
$R(\infty)$
$R(0)$
ν
ED_{50}
ED_{01}
Response
Dose
Parameters
$R(d)$ = Expected response
d = dose
b = background response
k = ED_{50}
n = Hill coefficient

United States Environmental Protection Agency

Point of Departure

- The point on a dose-response curve established from experimental data, e.g., the benchmark dose, generally corresponding to an estimated low effect level (e.g.,1% to 10% incidence of an effect).
- Depending on the mode of action and available data, some form of extrapolation below the POD may be employed for low-dose risk assessment
- POD may be divided by a series of uncertainty factors to arrive at a reference dose.

United States Environmental Protection Agency

Response

- Quantal
  - Incidence of disease or toxicity
  - Can be described as a percent (ED_{50})
- Continuous
  - Clinical, biochemical, physiological
  - Can be described as a percent (ED_{50}) but it is percent of maximum
    - Bench Mark Response
      - Some defined response related to adversity
      - One standard deviation from control
      - Percent of maximum response

United States Environmental Protection Agency

Limitations and assumptions

- Any model is an a optimized approximation of the true dose response from the available data.
- Dose # and spacing can have a big impact on the parameter estimates.
  - Choice of metric can define the spacing
- Ill defined maxima can lead to highly variable ED estimates
  - E.g For incidence data Max =100%, is this true?
- Background response impacts ED estimate.
  - Zero dose is not always zero exposure

United States Environmental Protection Agency

Criteria for Study Inclusion in Modeling Analysis

- 3 dose groups and a control
- Data presented in a table
- In some cases we contacted author for the data

> 300 Endpoints from 36 published manuscripts

  - Single-dose (administration)
  - Multiple repeated dose (administration)

- Response Categories
  - Biochemical
  - Hepatic
  - Immune
  - Retinol
  - Thyroid
  - Tissue
  - Toxicity

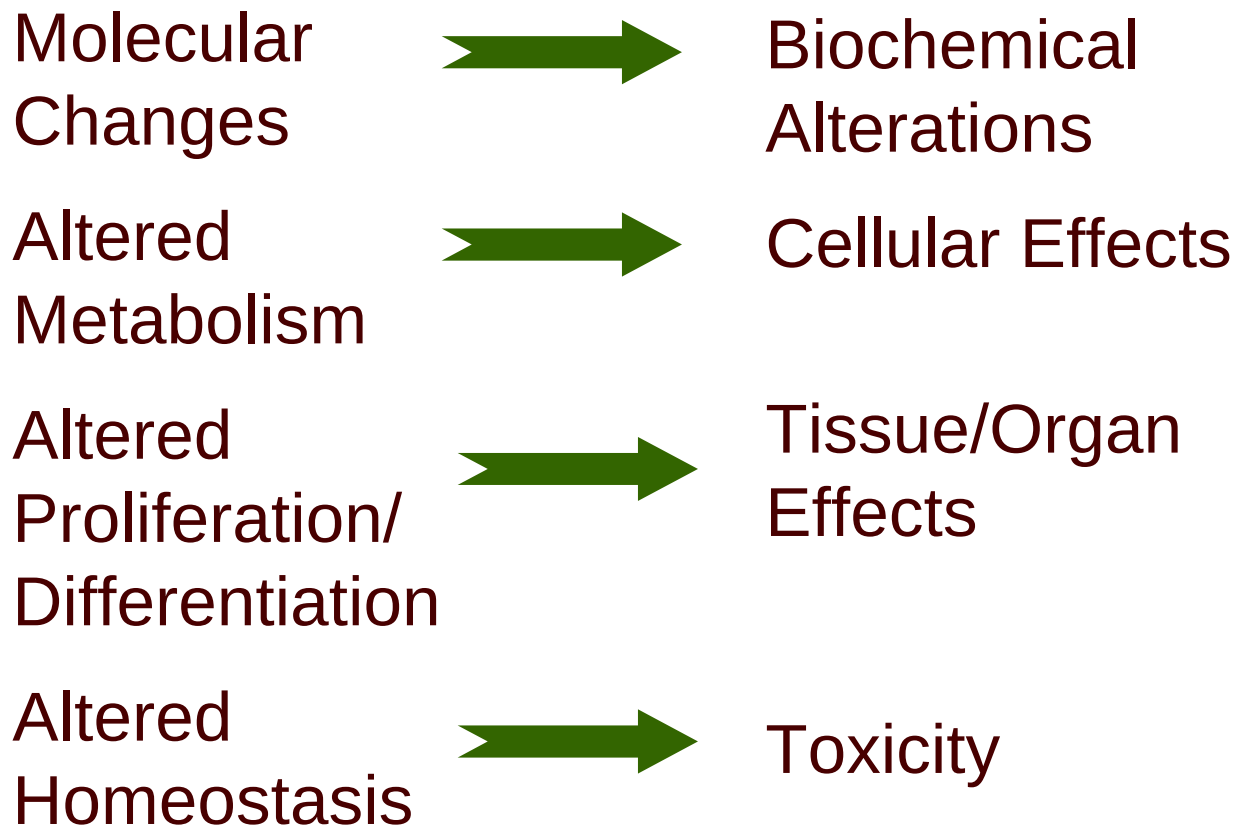
United States Environmental Protection Agency

Summary of Included Data

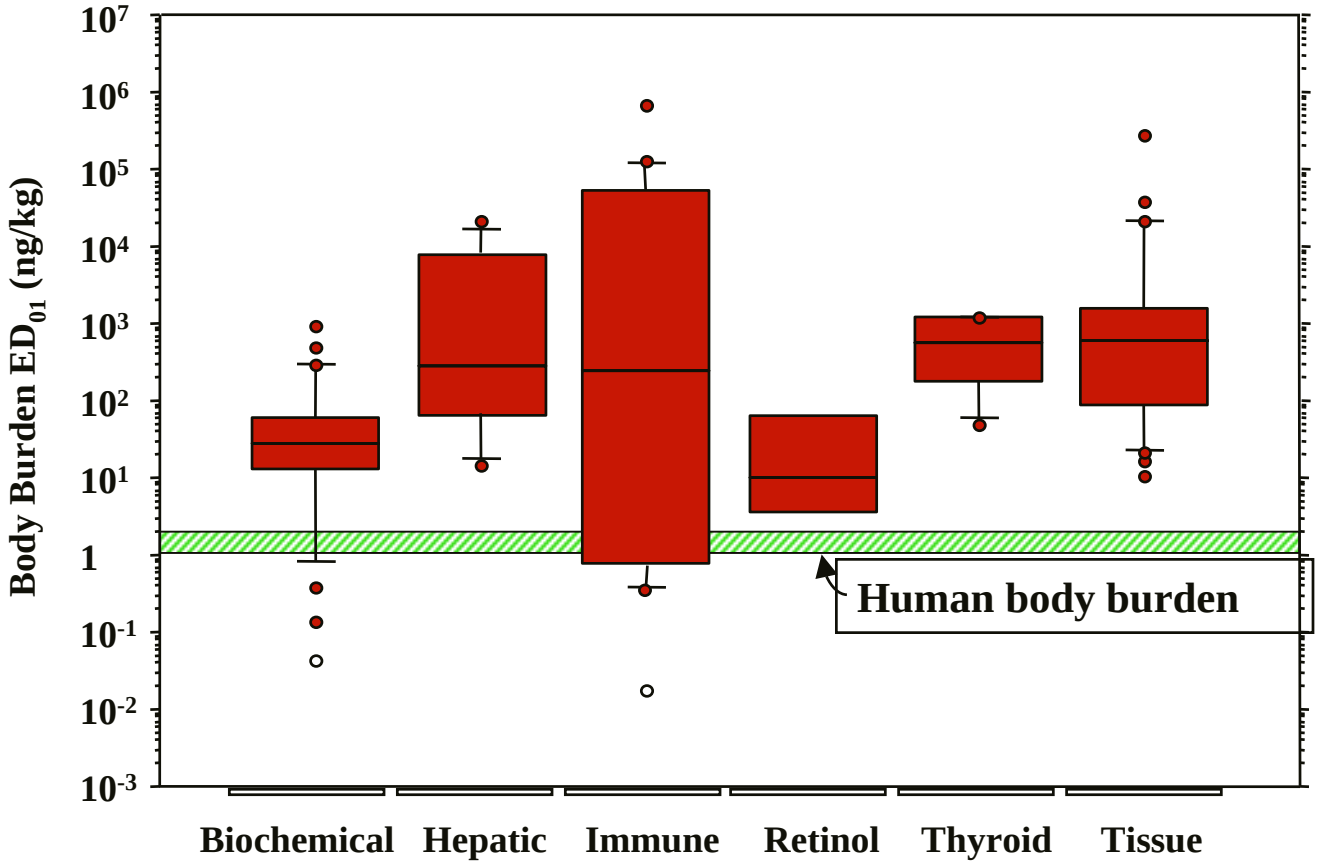
- 234 Responses with good model fits
  - 43% Multiple-dose studies
  - 32% Single-dose adult studies
  - 25% Single-dose developmental studies
- Species comparison
  - Rat (52%)
  - Mouse (47%)
  - Hamster (<1%)

United States Environmental Protection Agency

Effects of Dioxins



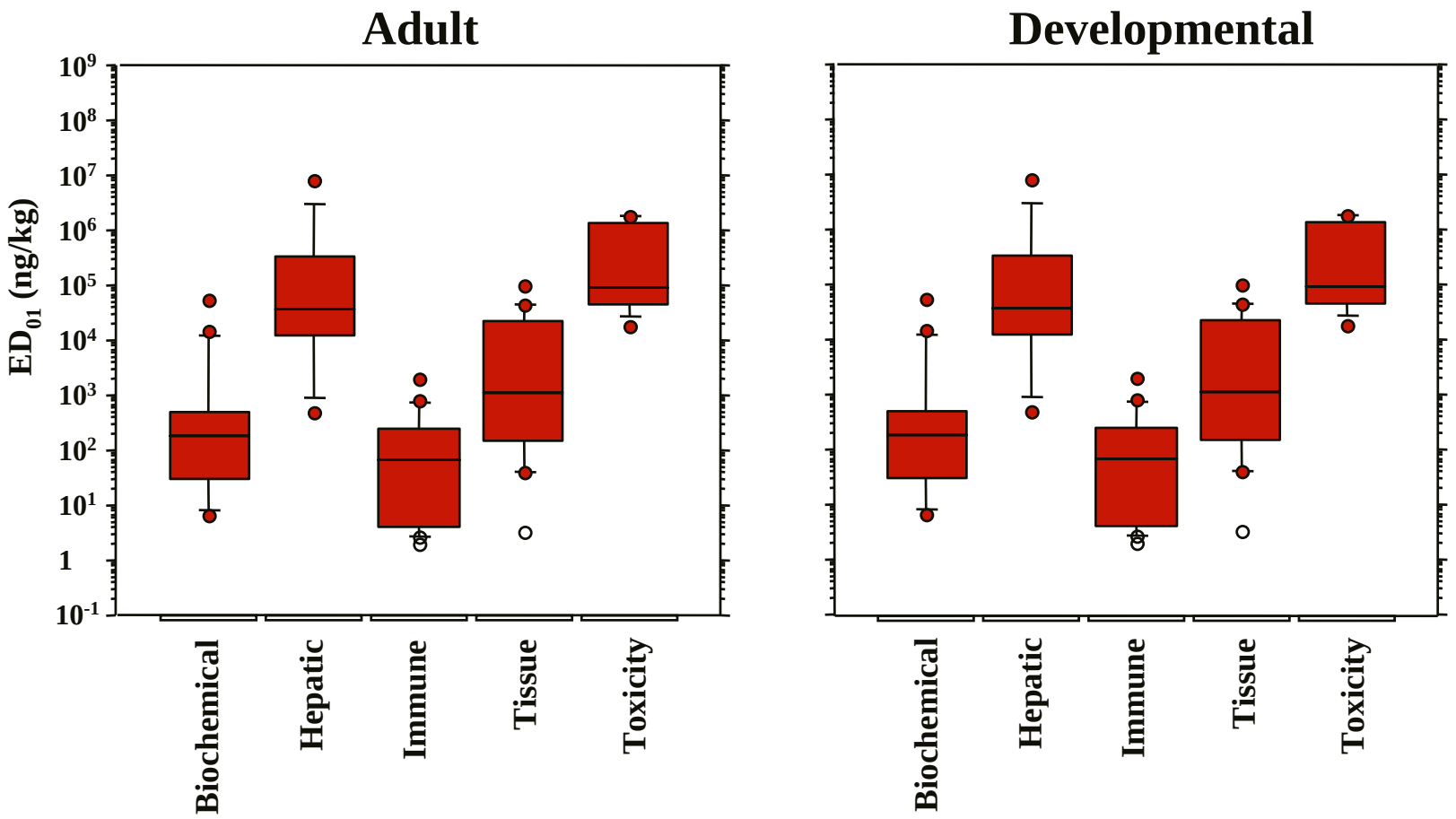
Body Burden Values at the ED01



Assuming steady-state conditions, body burden calculated:

ED_{01} (ng/kg body burden) = ED_{01} (ng/kg/day) * half-life/ln(2) * f

EDs01 for Single-Dose Studies



United States Environmental Protection Agency

Shape of Dose Response

- 40% of all responses examined were linear: Hill coefficient < 1.5
- Study Type Comparison
  - Multiple-dose: 43% linear
  - Single-Adult: 43%
  - Single-Developmental: 30%
- Category Comparison
  - Retinol: 100%
  - Thyroid: 50%
  - Immune, Tissue, Biochemical: 40-45%
  - Hepatic: 27%
  - Toxicity: 20%

United States Environmental Protection Agency

Conclusions

- EDs01/10 highly variable within and across response categories
- In general, half of the TCDD-induced responses support linearity and half non-linearity

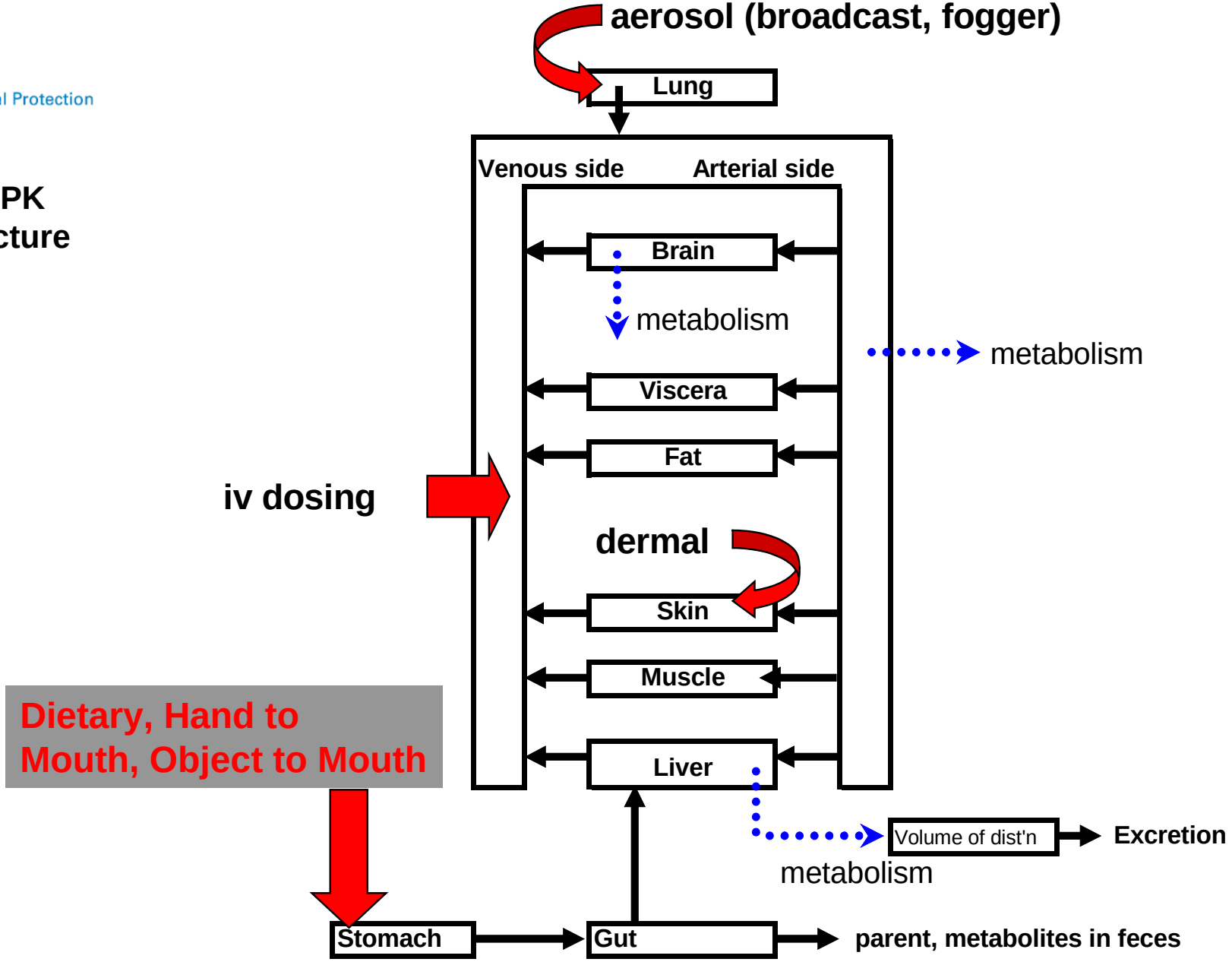
United States Environmental Protection Agency

Mechanistic Modeling

- Physiologically-Based Pharmacokinetic (PBPK) models
- Biologically-Based Dose Response (BBDR) models.

United States Environmental Protection Agency

Generic PBPK model structure



United States Environmental Protection Agency

Pharmacokinetics of dioxins

- Metabolism
  - Limited
- Lipid partitioning
  - Body fat mass: important at low exposures
- CYP1a2 sequestration
  - Observed in animals and humans
  - More important at high exposures
  - CYP1A2 may play a role in metabolism

Increasing evidence that elimination is dose dependent

United States Environmental Protection Agency

Comparison of initial blood concentrations determined by first order elimination or by PBPK model in 10 Ranch Hand Veterans

Groups	C_{blood} in 1982 measured [pg/g lipid adjusted]	C_{blood} at the time discharge from Vietnam estimated using constant T½ [pg/g lipid adjusted]	C_{blood} at the time discharge from Vietnam estimated using a PBPK model [pg/g lipid adjusted]
Low	12.7	53	138
	16.7	44	166
	23.5	72	277
	24.6	112	587
	25.0	83	168
High	33.7	103	492
	43.8	123	197
	115.5	381	6622
	182.3	602	40376
	209.7	640	35412

United States Environmental Protection Agency

Cancer Modeling

- Empirical
  - Ott and Zober (1996) (Hamburg cohort)
  - Flesch-Janys et al (1998)
  - Steenland et al (2001) (NOISH cohort)

- Mechanistic
  - Single initiated phenotype
  - Two initiated phenotype

United States Environmental Protection Agency

Summary of Empirical Models

- Epidemiological data not sufficient to mandate a particular model shape, including linear

- These analyses assumed a first order elimination rate of approximately 7 years in order to back calculate to the initial exposures

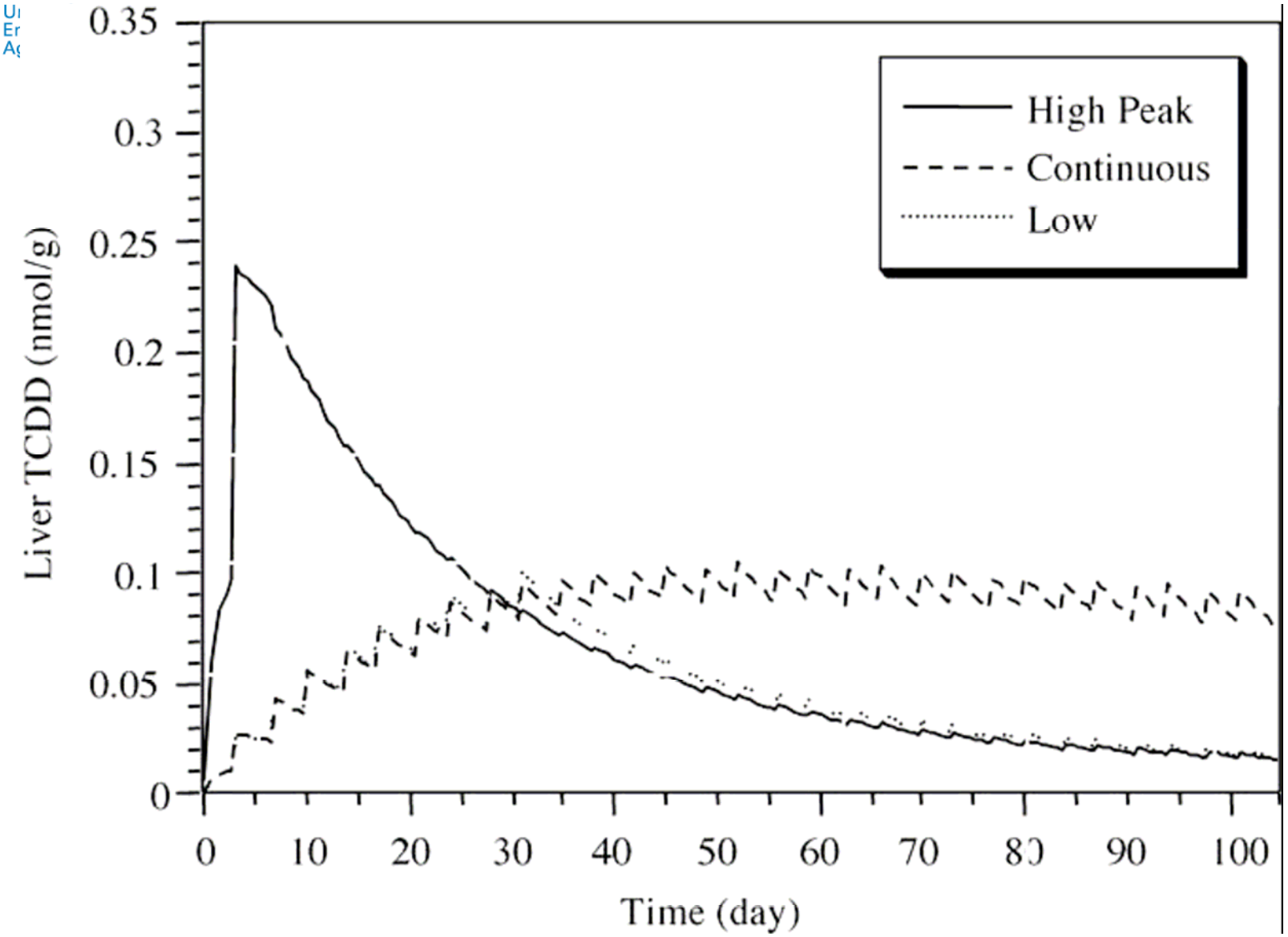
- If the pharmacokinetics of TCDD are not first order, these assumptions are not valid and could lead to misleading results on the shape of the dose response relationships. (Cheng et al, 2006)

United States Environmental Protection Agency

Kim et al (2003) Study Design

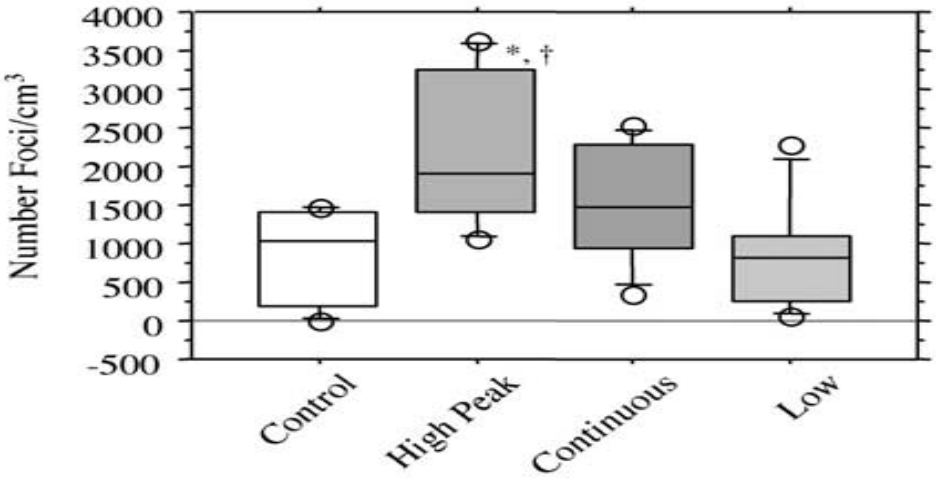
- Female Sprague Dawley rats
- Initiated with necrogenic dose of DEN
- Dioxin exposure started 2 weeks after DEN initiation
- Study terminated after 15 weeks

Exposure paradigm from Kim et al 2003

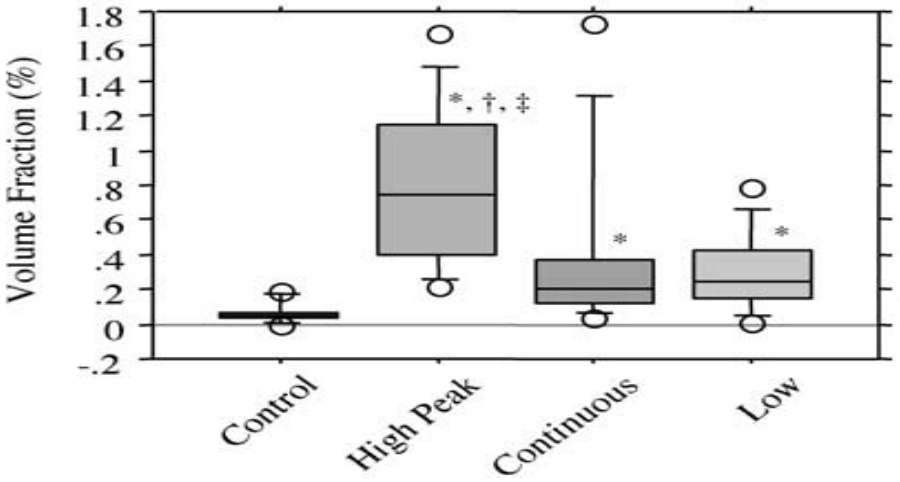


United States Environmental Protection Agency

(A)



(B)



United States Environmental Protection Agency

NTP TEF study

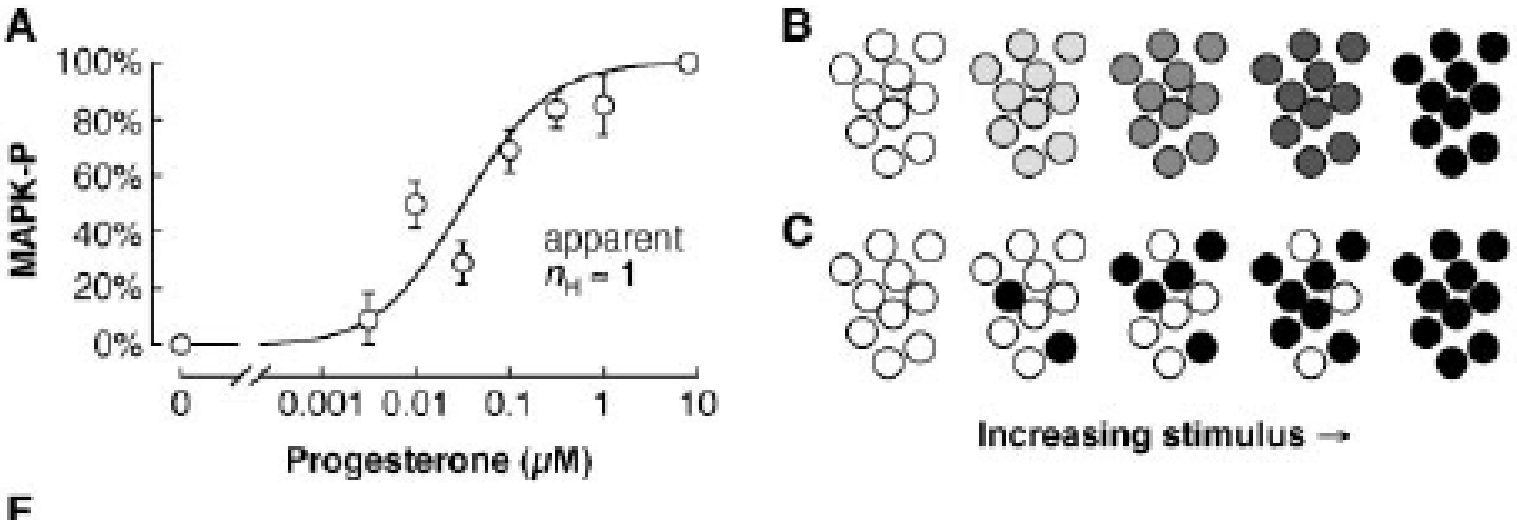
- 2-yr bioassay on TCDD, 4-PeCDF, PCB126,
- TEF method predicted liver tumors in SD rats for a mixture of TCDD, 4-PeCDF and PCB126 (Walker et al 2005)
- For TCDD all tumors had non-linear dose response relationships

United States Environmental Protection Agency

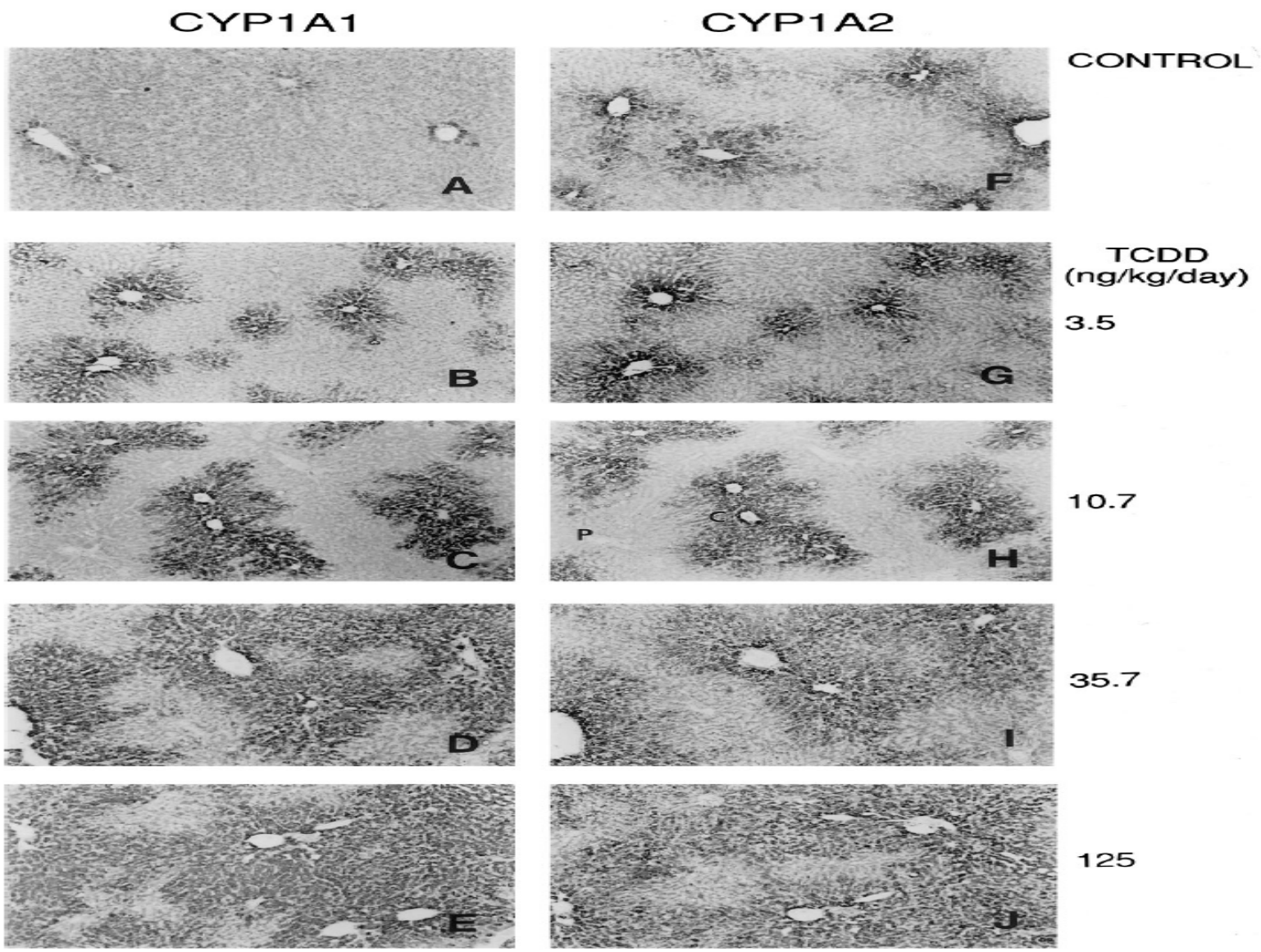
Mechanistic Modeling

- Single initiated Cell Model (Portier et al 1996; Moolgavcar et al 1996)
  - Assumes a single initiated phenotype
  - Predicts low dose linearity for cancer risk
  - ED01 approximately 3 ng/kg
  - Rat liver tumor model
  - Homogenous liver model (well mixed)

- Two initiated cell phenotype models (Conolly and Andersen 1997)
  - Spatial model
  - Rat liver tumor model



Ferrel and Machleder (1998)



Tritscher et al., 1992

United States Environmental Protection Agency

All or none Phenomena for CYP induction

- TCDD
  - Tritscher et al
  - Mills et al
- Phenobarbital
  - Jurtle et al.
  - others
- What about other biochemical changes?
- What are implications for toxicity and carcinogenicity?

United States Environmental Protection Agency

What can mechanistic modeling provide?

- Focus on one type of tumor – rat liver tumors
- In both humans and rodents we see multiple tumor types
  - Rats
    - Liver, lung, oral mucosa, others
  - Humans
    - All tumors
- Can mechanistic modeling inform on all of these tumor types?

United States Environmental Protection Agency

New Challenges since completion of latest version of the Dioxin reassessment

- Dose dependent pharmacokinetics
  - Potential impact on exposure estimates in epidemiological studies.
  - Michalek et al 2003; Aylward et al 2005
  - Potential to impact cancer risk (Cheng et al 2006)

- AUC as a dose metric (Kim et al 2003)
  - Suggests that AUC may not be the entire story.

ACKNOWLEDGMENTS

- National Research Council
  - Claude Emond
- NIEHS
  - Chris Portier
  - Nigel Walker
  - Fred Parham
- UNC-CH
  - Amy Kim
- USEPA
  - Bill Farland
  - Linda Birnbaum
  - Matt Lorber
  - Dwain Winters
  - David Cleverly
  - John Schaum
  - Linda Tuxen
  - Janet Diliberto
  - David Ross
  - Vicki Richardson