

# The U.S. EPA's Draft Oral Slope Factor (OSF) for 2,3,7,8-Tetrachlorodibenzo-*p*- dioxin (TCDD)

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# EPA 2005 Cancer Guidelines Extrapolation Approaches

- **Linear extrapolation is appropriate**
  - When agent has a mutagenic mode of action or acts through another mode of action expected to be linear at low doses, or
  - When data do not establish the mode of action, linear extrapolation from point of departure (POD) to origin is used as default option
- **Nonlinear extrapolation is appropriate**
  - When there is no evidence of linearity, and
  - When information is sufficient to support a mode of action that is nonlinear at low doses

# Cancer Assessment Approach

- EPA identified candidate cancer OSFs from 4 epi cohorts showing associations between TCDD and increased cancer or cancer mortality risk
  - NIOSH, Hamburg, BASF, Seveso
- EPA identified candidate cancer OSFs from 5 animal bioassays
  - Kociba et al. (1978), Toth et al. (1979), Della Porta et al. (1987), and NTP (1982, 2006)
  - Dose-response assessments performed for each individual tumor type and combined tumor incidences (Kopylev, 2009)
- EPA chose OSFs derived from the human data over the animal data as recommended by panelists at the 2009 Dioxin Workshop; consistent with 2005 Cancer Guidelines

# Draft Candidate Cancer Slope Factors

Human Occupational

Mouse

Rat

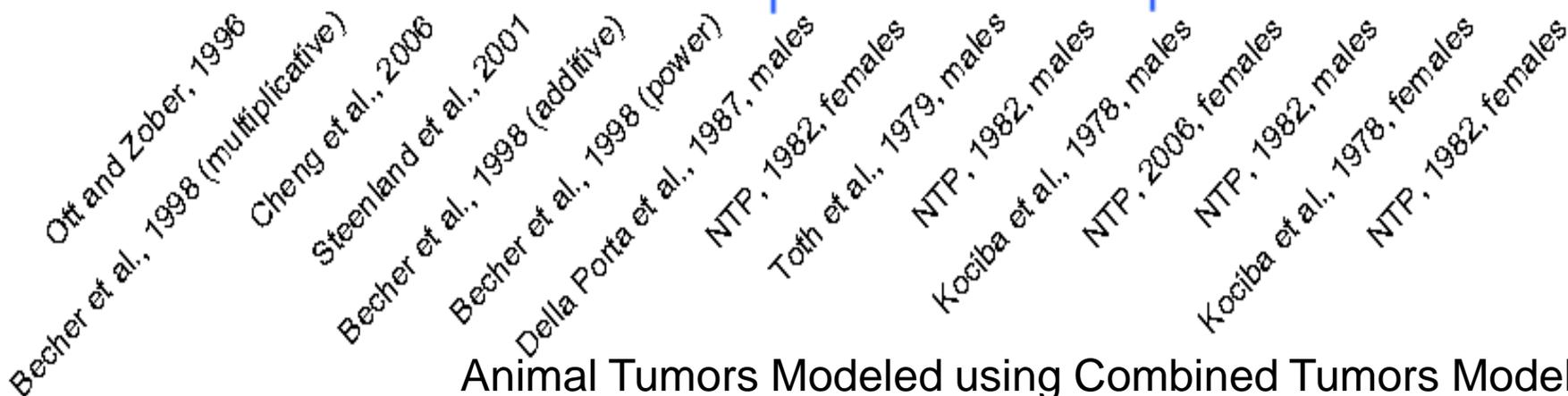
2,3,7,8-TCDD Slope Factor  
(per mg/kg-d)

1E+7

1E+6

1E+5

Draft candidate OSFs range from ~300,000-8,000,000 (mg/kg-day)<sup>-1</sup>



Animal Tumors Modeled using Combined Tumors Model

# Draft Candidate Cancer Slope Factors

Human Occupational

Mouse

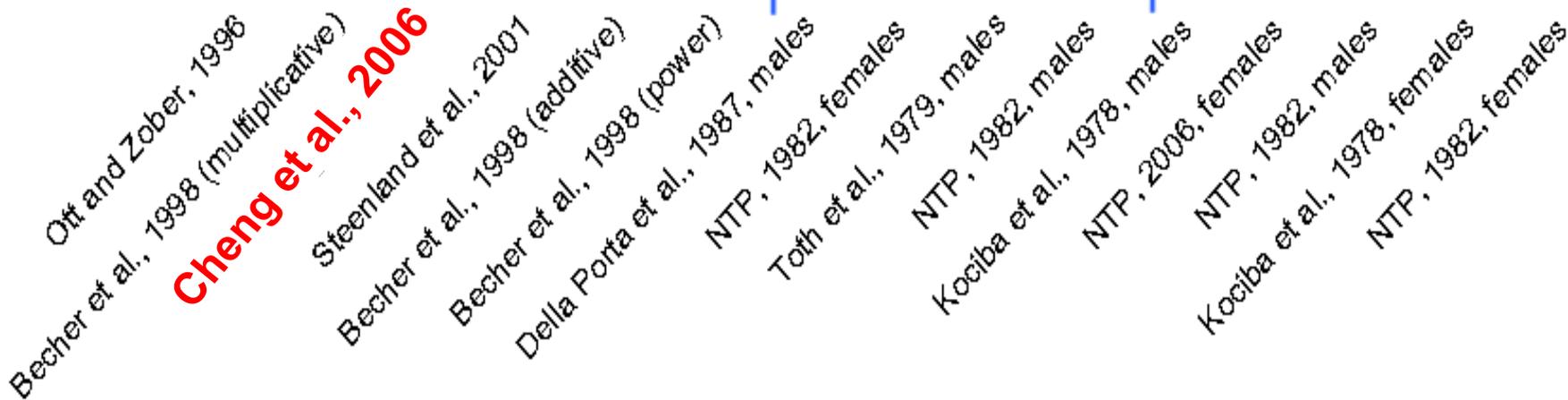
Rat

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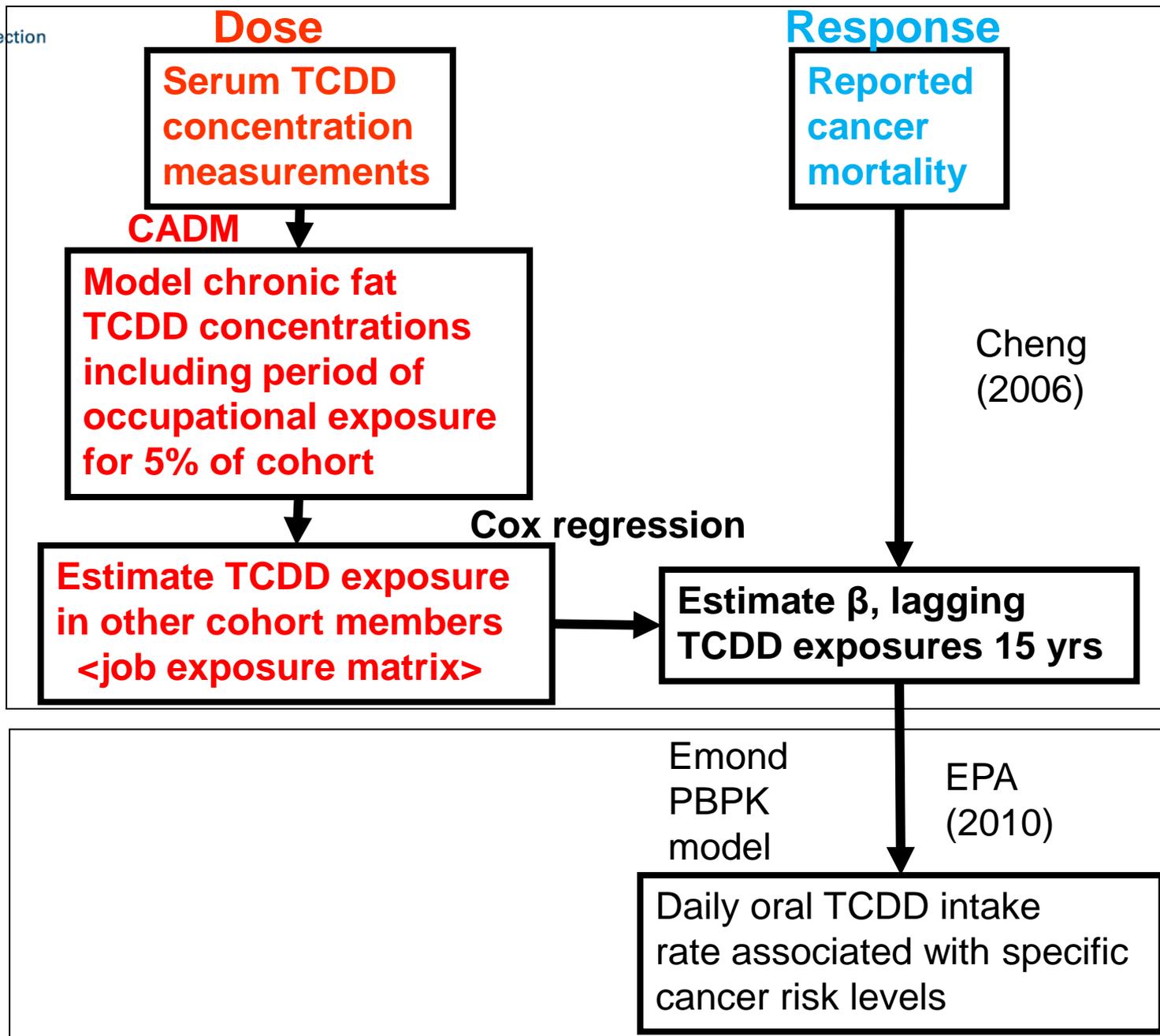
1E+5



# Cheng et al., 2006 Overview

- Analyzed relationship between back-extrapolated TCDD dose and all cancer mortality in NIOSH occupational cohort
- Concentration- and Age-Dependent Elimination Model (CADM)
  - Effective TCDD half-life in the body varies based on exposure history, body burden, and an individual's age
  - Previous studies assumed a constant (7–9 year) half-life for TCDD
  - Time-integrated body burden estimates are ~5x greater than those obtained using constant first-order elimination
    - Smaller differences between the two methods at lower exposures
    - Used measured TCDD concentrations and occupational exposure data for 5% of cohort to estimate TCDD exposures to other cohort members
- Calculated chronic serum TCDD estimates (dose term) for use in multiple dose-response analyses

# Draft OSF: Modeling Overview



# Cheng: Multiple Cancer Dose-Response Analyses using Cox Regression

- Dose-response relationship plateaus at high exposures
  - In one analysis, Cheng excludes top 5% of exposed individuals
  - Steenland: plateau could result from
    - Exposure misclassification at high doses
    - Depletion of susceptible individuals
    - Saturation of receptor-mediated processes
  - EPA believes excluding top 5% likely better represents slope in region of curve where fatal cancers increase with dose; response in top 5% of exposures is unrelated to the dose-response relationship at low doses
- Cheng analyzed lagged and unlagged exposure estimates
  - Compared to unlagged, Cheng reports stronger relationship between cancer mortality and exposure metrics lagged 15 years
  - EPA chose the lagged analyses to, in part, reflect the time needed for fatal cancers to develop

# Cheng et al., 2006: Cox Regression Modeling Results

- EPA used the upper bound on the regression slope for defining the cancer mortality risk
  - Excluding top 5% of exposure estimates
  - Lagging exposures 15 years
    - Note that the model gives risk in terms of the logarithm of the rate ratio as a linear function of cumulative fat concentrations
- This represents the incremental increase in cancer mortality above the NIOSH cohort's background TCDD exposure (~5 ppt/yr TCDD fat concentration), rather than above zero
- Below POD, EPA assumed slope is linear, nonthreshold to origin

# EPA Draft TCDD OSF: Emond Human PBPK Model

- NIOSH cohort exposures are reported as lipid- adjusted serum concentrations and simulated as fat concentrations in Cheng because CADM simulates fat levels in all tissues as one compartment
- EPA calculated risk-specific doses (as daily oral TCDD intake) using the Emond human PBPK model for the lifetime-average TCDD fat concentrations corresponding to the fat-area under the curve predicted by the Cheng model
  - Relationship of fat and blood TCDD concentrations and TCDD intake is not linear in the Emond model
  - The nonlinearity occurs at high doses rather than low doses, due to dose-dependent, induced hepatic sequestration of TCDD, which results in less-than-proportional effective tissue concentrations at higher exposures relative to intake
  - The relationship between ingested dose and blood or fat TCDD concentration is virtually linear at low doses

# Comparison of Equivalent Oral Slope Factors Based on Upper 95<sup>th</sup> Percentile Estimate of Regression Coefficients of All Fatal Cancers Reported by Cheng (2006) for Selected Risk Levels

<b>Risk level</b>	<b>Risk-specific dose (ng/kg-day)</b>	<b>Equivalent oral slope factors (mg/kg-day)<sup>-1</sup></b>
$1 \times 10^{-2}$	$8.8 \times 10^{-2}$	$1.1 \times 10^5$
$1 \times 10^{-3}$	$2.9 \times 10^{-3}$	$3.5 \times 10^5$
$1 \times 10^{-4}$	$1.3 \times 10^{-4}$	$7.8 \times 10^5$
$1 \times 10^{-5}$	$8.9 \times 10^{-6}$	$1.1 \times 10^6$
$1 \times 10^{-6}$	$8.1 \times 10^{-7}$	$1.2 \times 10^6$
$1 \times 10^{-7}$	$7.9 \times 10^{-8}$	$1.3 \times 10^6$

Due to nonlinearities in the PBPK model and Cox Regression Modeling in Cheng, there is a nonlinear relationship between Risk and Dose at high doses.

# Uncertainties in EPA's Draft TCDD OSF

- Exposure estimates in the NIOSH Cohort
  - Estimated serum TCDD levels for the entire cohort based on samples from a subset (5%) of cohort collected long after the occupational exposures had occurred
  - Occupational vs. ingestion exposures
- Shape of the dose-response curve below exposure levels in the reference population
  - Reference population not zero TCDD; uncertainty in shape of the dose-response curve in low-dose region (<5 pg/kg-day)
- Uncertainty due to background DLC exposure; co-exposures to other occupational carcinogens
- OSF derived using cancer mortality, not cancer incidence data
  - Likely minor source of uncertainty as 5-year cancer survival rates at time of study relatively low

# Summary: Draft Cancer OSF

- Draft OSF based on total cancer mortality in occupational epi cohort
  - Prefer human to animal bioassay data
- Longer-term TCDD exposure/kinetic modeling approach provides more biologically relevant exposure estimates, compared to other epi studies
- Below the POD, EPA assumed the slope is linear, nonthreshold to origin
- Draft equivalent oral slope factor is 1,000,000 (mg/kg-day)<sup>-1</sup>, when target risk range is 10<sup>-5</sup> to 10<sup>-7</sup>