United States Environmental Protection Agency

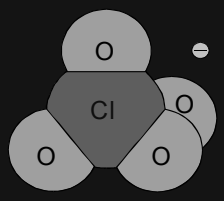
Office of Research and Development

# *Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization*

**US EPA Technical Support Project Semi-Annual Meeting**
**Denver, CO**
**June 4, 2002**

**Revised Assessment Highlights and Status**

Annie M. Jarabek
Special Assistant to the Associate Director for Health
National Center for Environmental Assessment




1

# 2002 Risk Assessment Authors

Randy Bruins, Ph.D.*
Harlal Choudhury, Ph.D.*
Tim Collette, Ph.D.
Kevin Crofton, Ph.D.*
Vicki Dellarco, Ph.D.*
David B. Dunson, Ph.D.
Andrew Geller, Ph.D.*
Michael Griffith, Ph.D.
Jean Harry, Ph.D.
Brian H. Hill, Ph.D.*
Gary Kimmel, Ph.D.*
Allan Marcus, Ph.D.*
Kevin Mayer*
Robert Park
John M. Rogers, Ph.D.
Ralph Smialowicz, Ph.D.*
Glenn Suter, Ph.D.*
Edward Urbansky, Ph.D.*
Douglas C. Wolf, DVM, Ph.D.

"The Right Stuff"

2

# 2002 Assessment Overview

- Assessment approach highlights
  - Process
  - 1999 External peer review recommendations
  - Conceptual Mode-of-Action Model
  - New studies and results: March 2002 review
    - Human health
    - Ecotoxicological
- Status: Next steps and emerging concerns
- Summary

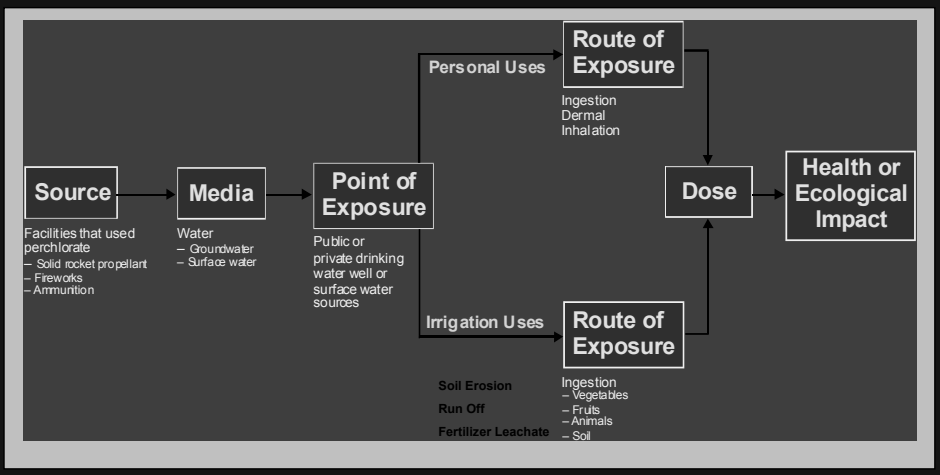
3


There is no drinking water standard at this time.

The 1999 ORD interim guidance of 4 to 18 ug/l (ppb) will stand until a new assessment is finalized.

Perchlorate was place on CCL as a research priority in all four (4) areas. Obviously the health area is being addressed by this assessment and analytical has evolved substantively as well. (Herman: PLEASE note that the current minimum reporting level (MRL) is 4 ppb with a minimum detection level (MDL) of 0.53 ppb. There is NO reason that IC method can't be improved to get MRL at 1 ppb and other methods show detection limits in sub-ppb range). Treatment tech also made progress -- CA has successful IX operation at large scale. UCMR and other surveys are already compiling needed occurrence and exposure data.

# ORD Goal: Comprehensive Characterization




**NCEA:** Health and Ecological Risk Assessments
**NHEERL:** Health Assessment Assistance
**NERL:** Analytical Methods Development and Exposure
**NRMRL:** Fertilizer Study and Analytical Methods Development

5

# Pro-Active Partnership

- March 1997; Expert peer review of an “RfD” presented by outside group concluded data inadequate for quantitative risk assessment
- Fall 1997; Congress mandated state-of-the-science determination in all areas -- EPA to work with governmental agencies
- January 1998; Interagency Perchlorate Steering Committee formed to address all areas
- DOD and PSG partnered with EPA to develop targeted testing strategy based on mode of action for perchlorate: health and eco screen
- Development of health and eco data base with DOD/PSG dollars in 2 years sufficient to support first EPA external peer review

6


The development of understanding, methods and characterization for all these efforts (occurrence, analytical, treatment technology), and particularly for the health and eco risk assessments, were accomplished in an expedited fashion through the unique partnership of several governmental entities. The Department of Defense, notably the Air Force Research Laboratory, and the consortium of defense contractors known as the Perchlorate Study Group funded the major studies that will be the subject of review today. The EPA wants to acknowledge their efforts and looks forward to future collaboration in extending the analytical methods and developing effective treatment technologies.

Each laboratory (NHEERL, NRMRL and NERL) in addition to NCEA within ORD, the program offices (OW and OSWER) and all the regional offices within EPA were engaged in addressing the contamination and contributed to the assessment presented here today. The NIEHS and NIOSH were both strong collaborators on the reviewing and evaluating these data (firewall issue -- could comment that per typical we are caught in the middle -- ha ha) and risk assessment approaches.

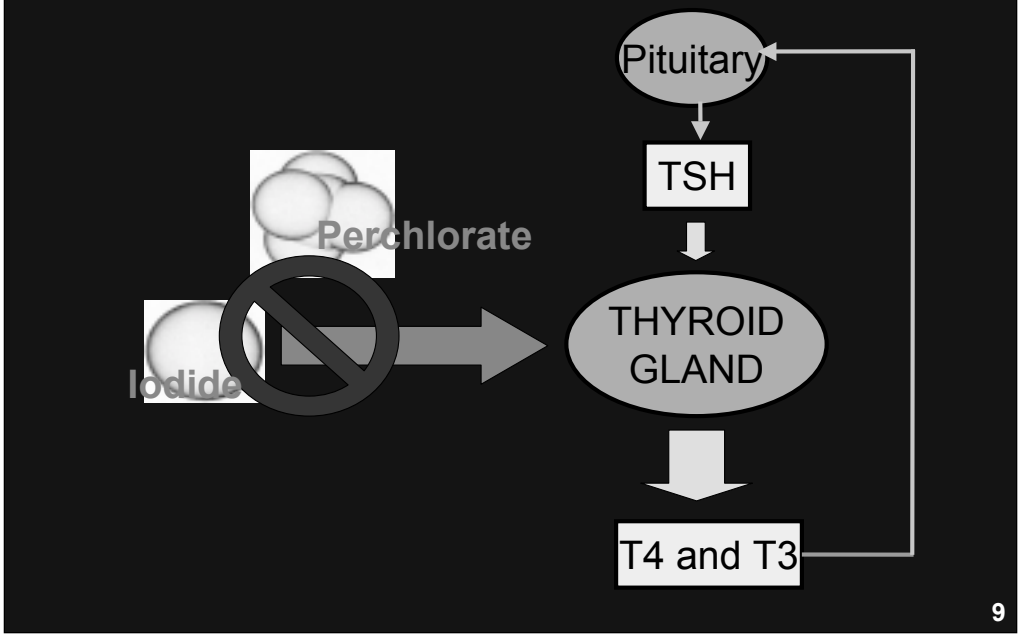
The Interagency Perchlorate Steering Committee (IPSC) was formed in January 1997 to bring governmental (AGAIN PSG NOT A MEMBER) representatives and affected state, tribal and local governments together. Serves as a clearinghouse for accurate account of the state of the science and technology transfer / communication for the key areas of concern.

# US EPA Assessment Process

- December 1998; NCEA published external peer review draft
- February 1999; Public peer review workshop
- Response to recommendations re: additional studies and analyses
  - New data on neurodevelopmental, thyroid histopathology, neoplasia, immunotoxicology, PK and ecological receptors
  - PWG and NIEHS analyses
- Revised assessment based on recommendations under Agency internal review
  - Expedited CalEPA collaboration for alignment

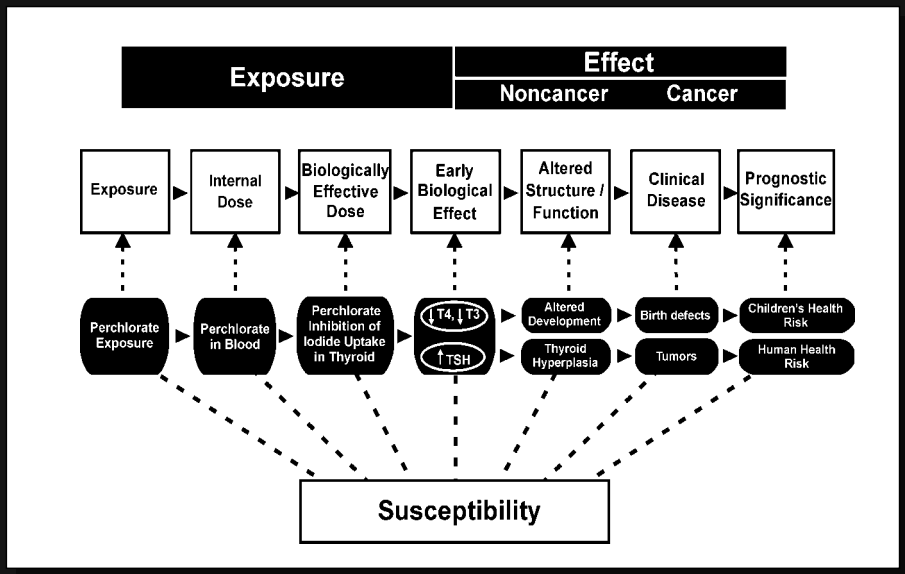
8

# Perchlorate Mode of Action




9

# Proposed Mode-of-Action Model for Health Risk Assessment of Perchlorate




10

# 1999 External Peer Review

- Basis of health assessment
  - Thyroid histopathology in PND5 rat pups
  - Histopathology used as biomarker for adverse hormonal changes *in utero*
- Screening level ecotoxicological assessment
  - Agreed with characterization
  - Identified additional data gaps
- Scientific expert peer findings
  - Concurred with conceptual model and nonlinear approach
  - Supportive of concern for neurodevelopmental
  - Provided recommendations

11

# 1999 Peer Review Recommendations

- Evaluate variability in RIA kits across laboratories
- Pathology Working Group of thyroid histopathology
- Additional brain morphometry if material available
- Developmental study in rats
- Repeat motor activity study in rats
- Repeat and additional immunotoxicity studies in mice
- Pharmacokinetic information in humans and rats
- Alternative statistical analyses for hormone data
- Chronic ecotoxicological studies
- Additional ecotoxicological receptors
- Data on transport and transformation

12

# New Studies: Humans

- Observational (ecological) epidemiological studies
  - Not part of testing strategy
  - Limited exposure measures, demographic data, population size and outcome measures
  - Lack of control for confounding
- Clinical studies
  - 3 different laboratories
    - Greer et al. (2000; 2002 - In Press)
    - Lawrence et al. (2000) and (2001)
    - Unpublished data from Drs. H. Leitolf and G. Brabant
  - EPA had limited input on one (Greer et al., 2000; 2002) at outset; designed with intent to provide pharmacokinetic information and not to designate effect levels
  - Those that underwent QA/QC used by AFRL to develop human PBPK model and others to support validation

13

# EPA Interim Human Study Policy

- Federal agencies adhere to “common rule” guidance that includes informed consent
- Agency has long-standing concern for “third-party” human data
  - Intentional dosing with toxicant to determine effect levels
  - IRB information often unavailable
  - Issue is how to ensure adherence on *post hoc* basis
- Moratorium issued on December 14, 2001 re: use of this type of data **in the future** until the NAS determines criteria for acceptability
  - Human studies were considered and shortcomings noted in assessment
    - Studies not used to determine hazard based on human NOAEL
    - “What if” calculation was provided
  - Human data were used to support the AFRL PBPK model

# New Studies: Laboratory Animals

- Pathology Working Group (PWG) of previous data
  - Thyroids: colloid depletion, hypertrophy, hyperplasia
  - Brains: Insufficient materials
- AFRL interlaboratory study of RIA kits to measure hormones evaluated across 3 laboratories
- Argus 1999 two-generation reproductive study in rats
- Argus 2000 developmental study in rats
- USN (Bekkedal et al., 2000) motor activity study in rats

15

# New Studies: Laboratory Animals

- "Effects study" protocol in rats (Argus, 2001)
  - Hormones and thyroid histopathology in pups and dams
  - Brain morphometry
- Immunotoxicity study in mice
  - Repeat macrophage phagocytosis
  - Sheep red blood cell (SRBC) assay of humoral immunity
  - Contact hypersensitivity

16

## New Studies: Ecotoxicology & Exposure

- Acute (EA Engineering, 1999)
  - *Selanstrum caprinconutum* 96-hr
- Subchronic ecoxoticity (Block Env. Svcs., 1998)
  - Pimephales promelas 7-day
- Chronic ecotoxicity (Block Env. Svcs., Inc., 1998; EA Engineering, 2000)
  - *Pimephales promelas* 35-day Early Life Stage
  - *Hyalella azteca* definitive 28-day study
  - *Ceridaphnia dubia* 6-day
- FETAX studies
  - Dumont and Bantle, 1998
  - Goleman et al., 2002

17

# New Studies: Ecotoxicology & Exposure

- Six site-specific occurrence & biotransport studies (Parsons Engineering, 2001)
  - Site media
  - Various ecological receptors @ each site
- Phytotransformation and plant uptake studies
  - Nzengung et al., 1999; Nzengung and Wang, 2000
  - Susarla et al., 1999; 2000
- Occurrence & biotranport studies
  - US Army Corps of Engineers (Condike, 2001): fish
  - Smith et al., (2001): water, sediments, vegetation, fish, mice
- Indirect exposure characterizations
  - EPA Fertilizer study with The Fertilizer Institute (US EPA, 2001a,b)
  - Wolfe et al., 1999; Ellington et al., 2001; Urbansky, 2000

18

# Designation of Effect Levels

- Thyroid histopathology
  - Benchmark response @ 10%
  - BMDL used as NOAEL surrogate in RfD derivation
- Thyroid hormones
  - Response level @ 10%
  - Analysis of Variance (ANOVA)
- Brain morphometry
  - Repeated measures issue — T-tests inappropriate
  - Profile analysis
    - Mulitvariate analysis of variance
    - Vector does not require expectation on magnitude or direction
  - Issues on sectioning addressed with restricted analyses
    - PND21
    - Sidedness, normalization, region and level

19

# Designation of Effect Levels

- Motor activity data from Argus 1998 DNT and USN
  - Bayesian hierarchical analysis with linear mixed-effects regression
  - Individual studies and data combined
  - Results indicate effects @ 1 mg/kg-day
- Thyroid tumors in Argus 1999 two-gen study
  - 3 tumors in 2 animals @ 19 weeks in F1 adults
  - Compared to incidence of all thyroid tumors in NTP archives for SD-rats @ 2-year bioassay terminal sacrifice
  - Bayesian analysis
  - Results indicate concern for *in utero* programming
    - Latency
    - Incidence

20

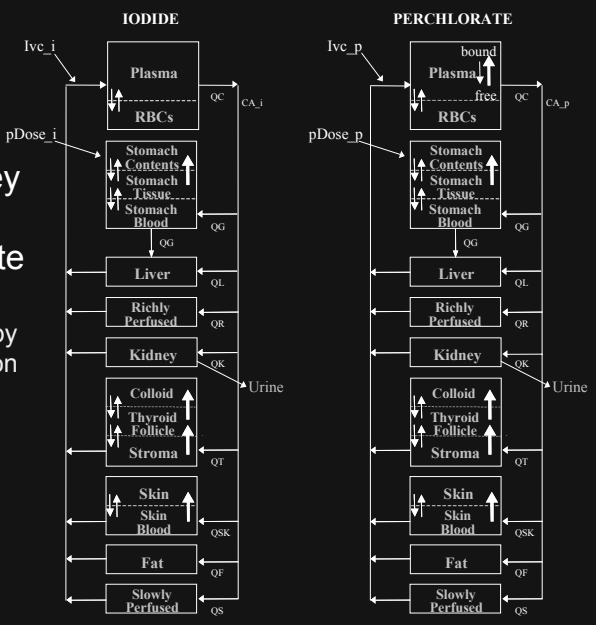
# Point of Departure

- Key event defined as an empirically observable precursor step that is a necessary element or marker for mode of action
- Identified as iodide uptake inhibition @ the $Na^+$-$Iodide^-$ Symporter (NIS)
  - Reinforced by repeat studies showing neurodevelopmental effects
  - Precursor for thyroid hormone perturbations
  - Allows harmonization in approach to address neurodevelopmental and neoplastic sequelae
- Weight of evidence for 0.01 mg/kg-day LOAEL
  - Thyroid and pituitary hormones
    - Dams on GD21
    - Pups on GD21, PND4 and PND9
    - 14-days and 90-day for T4 and TSH
  - Thyroid histopathology
    - Pups on PND4 in 1998 and 2001 and weanlings in 1999
  - Brain morphometry in pups on PND21

21

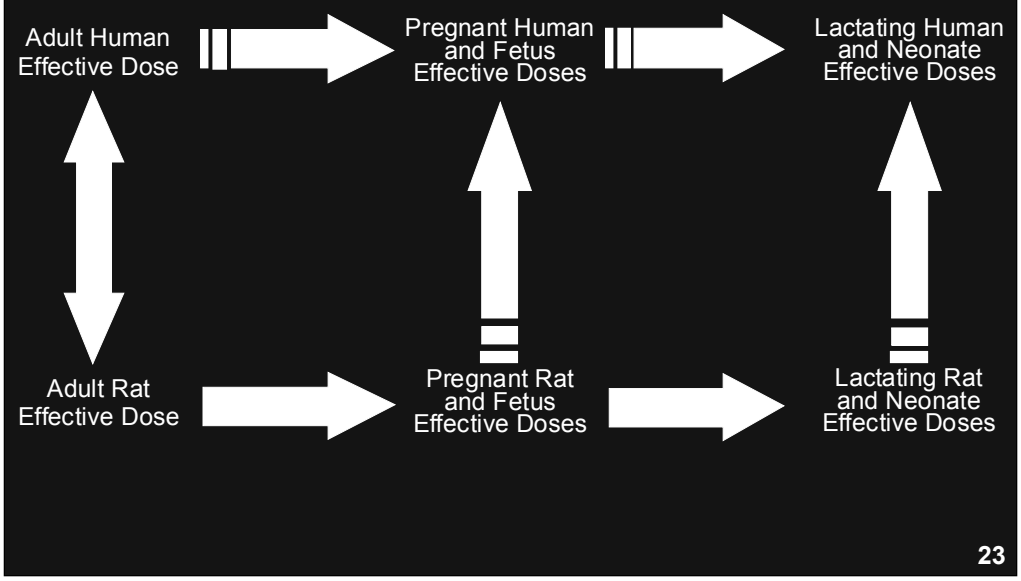
# AFRL Dosimetry Model Structures

- 4 Model Structures
  - Adult male rat
  - Adult human
  - Pregnant rat & fetus
  - Lactating rat & fetus
- Compartments for key tissues
- Iodide and perchlorate disposition
  - Active uptake described by Michaelis-Menten saturation
  - Permeability areas cross products and partitions
  - Passive diffusion
  - Plasma binding
  - Urinary elimination
- Growth



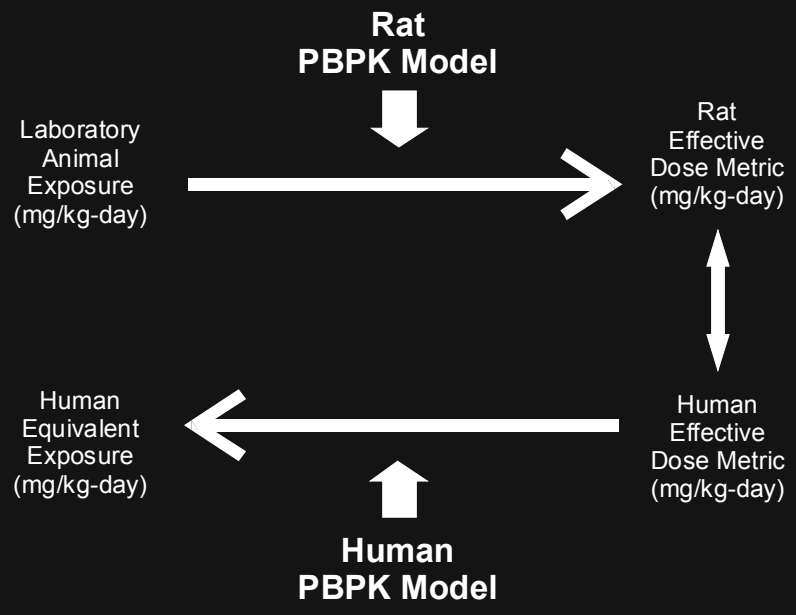

22

# Parallelogram Extrapolation

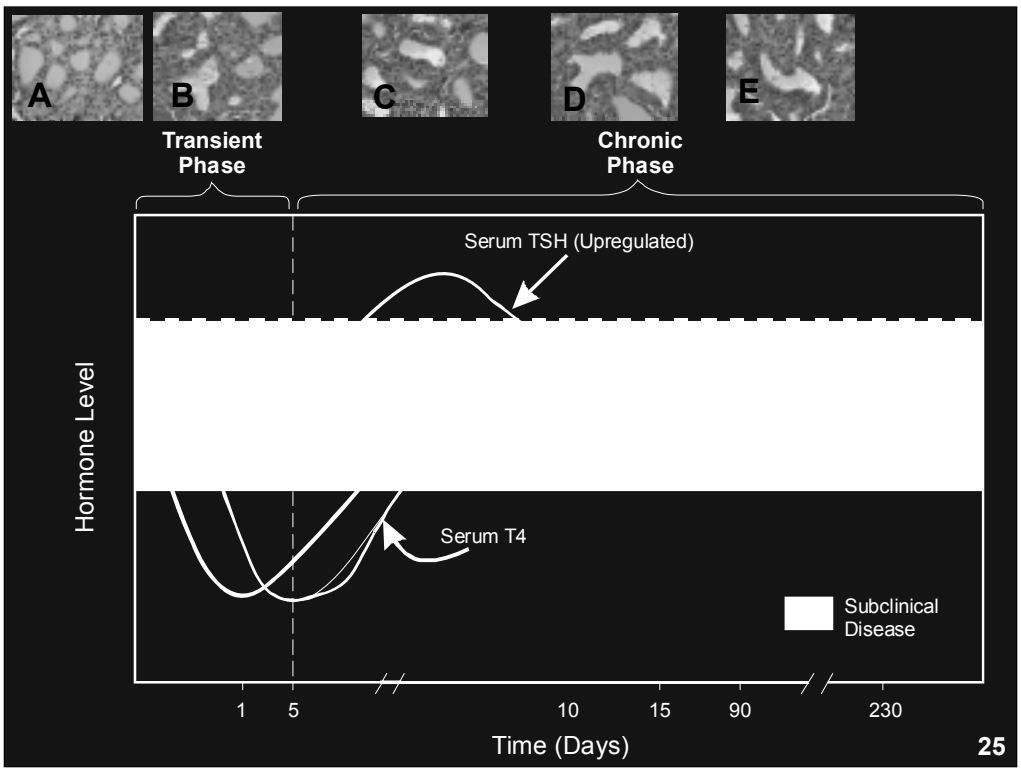



23

# Human Equivalent Exposure




24


A
B
C
D
E
Transient Phase
Chronic Phase
Serum TSH (Upregulated)
Hormone Level
Serum T4
Subclinical Disease
1
5
10
15
90
230
Time (Days)
25

# Choice of Dose Metric

- Internal perchlorate concentration as metric associated with key event of iodide inhibition
  - iv data in rats (“acute”)
  - Drinking water in humans
- Area Under the Curve in (AUCB) blood versus peak
  - Good correlation with iodide inhibition
  - Average of serum and thyroid
- EPA agreed with DOD re: uncertainty in and lack of validation of thyroid parameters notably in fetus and neonates for iodide inhibition description
- HEE based on maternal AUC in blood at GD21

26

# Uncertainty Factors

- Composite factor of 300 parceled into components
  - Intrahuman: 3
    - Pharmacokinetic variability
    - Not representative of sensitive populations
  - Interspecies: None
    - PBPK dosimetry model for extrapolation
  - LOAEL to NOAEL: 10
    - Hormones (slope), thyroid histopathology and brain morphometry
    - Interdependence with lack of interspecies and choice of dose metric
  - Subchronic to chronic duration: 3
    - Lack of "womb to tomb" design and *in utero* programming concern — recalibration of HPT feedback system
    - Interdependence with intrahuman factor
  - Database Insufficiencies: 3
    - Concern for immunotoxicity reinforced

27

# Operational Derivation

RfD (mg/kg-day) = 0.01 x 0.85 ÷ 300 = 0.00003

Where:

- 0.01 is the point of departure
- 0.85 adjusts to perchlorate anion alone
- 300 is the composite uncertainty factor

28

# Comparative Risk Derivations

- "What if" calculation based on human data
  - 0.007 mg/kg-day
  - Uncertainty factor of 100 parceled as:
    - Intrahuman variability: 3
    - LOAEL to NOAEL: 3
    - Subchronic to chronic duration: 3
    - Database insufficiency: 3
  - Result is 0.00007 mg/kg-day
- If a larger UF was applied for intrahuman variability then resultant estimate would be essentially equivalent to that proposed

29

# Comparative Risk Derivations

- Derivation based on tumor precursor lesions
  - Colloid depletion, hypertrophy and hyperplasia all observed @ > 0.3 mg/kg-day
  - BMDL estimates of 0.9, 0.15 and 0.0004 mg/kg-day
  - HEE estimates of 0.45 and 0.02 for colloid depletion and hypertrophy
  - Uncertainty factor of 100 parceled as:
    - Intrahuman variability: 3
    - LOAEL to NOAEL: 3
    - Subchronic to chronic duration: 3
    - Database insufficiency: 3
  - Result is in range of 0.005 to 0.0002 mg/kg-day
  - A larger UF for intrahuman variability would result in 0.002 to 0.00007 mg/kg-day

30

# Hypothetical RfD Conversion

- Critical to distinguish the RfD from any guidance value that may result
- Conversion to drinking water equivalent level (DWEL) in ug/L (ppb):
  - Adjustment by 70 kg and 2 l
  - DWEL = 1 ug/l (ppb)
- Derivation of maximum contaminant level goal (MCLG) typically involves the use of a relative source contribution (RSC) factor to account for non-water sources of exposures
  - Range of 0.2 to 0.8
  - Default @ 0.2 when data are inadequate to determine
  - Result would be MCLG between 0.2 to 0.8 ug/l (ppb)

31

# Now versus Then: RfD

- New studies tested a 10-fold lower dose, repeat studies reinforced neurodevlopmental sequelae, and concern for *in utero* effects emerged
- Provisional range of 0.0001 to 0.0005 mg/kg-day and revised RfD @ 0.00003 mg/kg-day
- RfD is **not a standard.** If convert to drinking water equivalent level (DWEL):
  - Adjustment by 70 kg and 2 L consumption
    - *Provisional; 4 to 18 ug/L (ppb)*
    - *Revised; 1 ug/L*
- Convert DWEL by relative source contribution (RSC)[20 to 80%] to MCLG

32

# Ecotoxicological & Exposure

- Screening-level and not definitive
- Exposure issues:
  - Accumulation in terrestrial and aquatic plants
  - Fate in irrigated soils
  - Potential for dietary toxicity to vertebrate herbivores point to need for lower limits of detection in plant and animal tissues
- Effects need determination:
  - Exposure on aquatic plants and noncrustacean invertebrates
  - Dietary exposures in birds and in herbivorous or litter-feeding invertebrates
  - Dietary and cutaneous exposure for adult amphibians and aquatic reptiles

33

# Purpose of IRIS Peer Review

- Provide peer review of protocols, performance, and results reported in studies since 1999 that have not appeared in the open literature
- Provide individual expert comment on EPA external review draft regarding approach, analyses, and inferences used in the human health and ecological risk assessments
  - Panel was ***NOT*** charged with arriving at a consensus opinion or conclusion
  - Public and observer comments incorporated according to professional judgement of panel
  - Comments related to EPA policy or potential rulemaking are ***NOT*** relevant to scientific review

34

**Remember to note** on second sub-bullet about individual peer reviewers can pursue extended dialogue if they so desire when compelled by public comments

# Emerging Assessment Concerns

- DOD/PSG expectation was that RfD would increase with additional data -- scale of contamination means considerable cleanup costs
- New epidemiological data, EWG July 2001 report and Cal PIRG raised concern about neuropsychological deficits
- Potential for bioaccumulation and indirect exposures need to be characterized
- Proposed EPA RfD driven by key events/precursor lesions for neurodevelopmental and new concerns for neoplastic sequelae in neonates
- July 2001; CalEPA proposed PHG results in same range

35

# Risk Assessment Status

- Document on web January 18, 2002 with a reference CD available: http://www.epa.gov/ncea.
- Public comment period extended until April 5, 2002
- Draft peer review report back to the panel and to the Agency end April 2002
- Final external peer review report end May 2002
  - Posted on the EPA web in June, 2002
  - Agency is responsible to respond to comments and disposition of major comments will be indicated
- Submit revised final draft document to IRIS Agency consensus review in fall 2002
- Final changes in response to Agency review
- Expect IRIS clearance with final document posted to IRIS in late fall 2002 or early 2003

36

# Summary: Unique Attributes

- Pro-active partnership to develop data
- Testing and assessment model motivated by mode of action
- Harmonized approach to noncancer and cancer toxicity based on key event
- Both human and ecological risk assessment of available data
- Evaluation of indirect exposure potential based on stakeholder concerns and to inform relative source contribution (RSC)
- Comprehensive characterization — integrated approach challenging
  - Analytical
  - Occurrence / exposure / transformation & transport
  - Assessment approaches
  - Treatment technology

37

# The Perchlorate Contamination Challenge

## Credible Science

## Credible Decisions

- Accurate risk characterization
- Appropriate management strategies

38