
PERCHLORATE: HUMAN HEALTH AND ECOLOGICAL EXPOSURE IMPACTS

Presented by:

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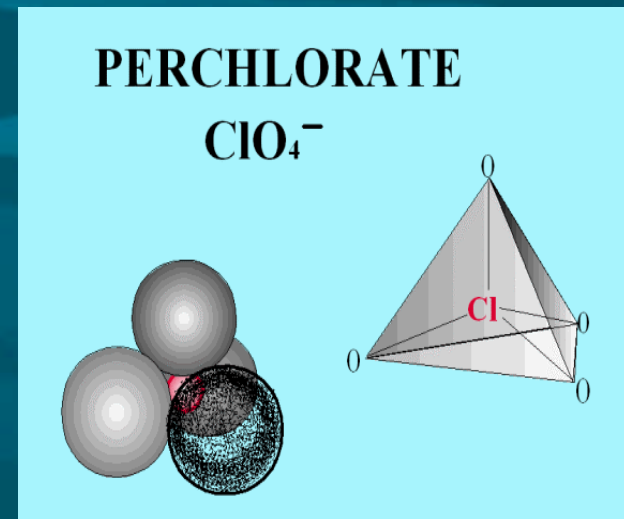


Introduction - Purpose

- n To provide an overview of the human health and ecological effects issues related to exposure to perchlorate
- n To provide a timeline of investigations into potential toxicity of perchlorate
- n To provide a synopsis of where the science is today

Introduction – Perchlorate

- n Anion
- n Originates from the solid salts of ammonium, potassium or sodium perchlorate
- n Highly soluble in water
- n Persistent in water



Introduction - Perchlorate

n Occurrence and Uses

- Naturally occurring and man-made chemical
- Can be found in vegetation and/or crops
- Occurs naturally in nitrate-rich mineral deposits used in fertilizers
- Primary ingredient of solid rocket propellant
- Salts also used as components of air bag inflators and in the manufacture pyrotechnics and explosives
- Laboratory waste by-products of perchloric acid



Introduction - Perchlorate

n Toxicokinetics

- In the body, readily absorbed upon ingestion, dermal and inhalation exposures not expected to be significant
- Primarily excreted unchanged
- Relatively short half-life (5-8 hours)



Perchlorate - Database

- n Human Health Effects Data
 - Clinical studies
 - Epidemiology studies
 - Occupational studies
- n Animal Studies
- n Physiologically Based/Pharmacokinetic (PBPK) modeling (extrapolation between species)
- n *In Vitro* studies (mode of action)

Perchlorate – Animal Health Effects Data

- n Immunotoxicity
- n Thyroid hormone levels
- n Brain morphometry
- n Neurotoxicity
- n Thyroid pathology
- n Reproductive toxicity
- n Developmental toxicity
- n Genetic toxicology

Overview – Mode of Action

- n The known mode of action for perchlorate is that it acts as a competitive inhibitor of active iodide uptake by the NIS [sodium (Na⁺)-iodide (I) symporter (S)] in animals and humans
- n This decrease in intrathyroidal iodide results in a decreased production of T3 and T4 thyroid hormones

Overview – Mode of Action

- n Perchlorate interferes with iodide uptake into the thyroid gland. Because iodide is an important component of thyroid hormones, perchlorate disturbs thyroid functions
- n In adults, the thyroid helps to regulate metabolism
- n In children, the thyroid plays an important role in proper development in addition to metabolism
- n May impact the fetus and newborn and result in neurodevelopmental effects
- n Changes in thyroid hormone levels may also result in thyroid gland tumors
- n EPA considers the inhibition of iodide uptake as the critical effect

Overview - Human Health Debate

- n Validity and relevance of laboratory animal data for use in risk assessment
- n Use of human data in risk assessment
- n Uncertainty
 - Sensitive sub-populations
 - Adaptive vs. adverse effects
 - Dose Response in humans – amount and duration of exposure

Timeline

1997

- n (April) Development of a low-level (4 ppb) detection method
- n Detected in:
 - Many states. Many locations
 - Drinking water, groundwater, surface water, soil
- n Peer review panel determined ecological & human health database inadequate for quantitative risk assessment
- n (May) Developed a testing strategy



Timeline

1998

- n (March) No National Primary Drinking Water Regulation (NPDWR)
- n Added to Office of Water (OW) Contaminant Candidate List
 - Noted need for additional research and information before regulation
 - Interagency Perchlorate Steering Committee (IPSC)
 - Representatives from 19 agencies. Includes: EPA, DOD, ATSDR, NIEHS, Native American Tribes and various state agencies
 - Identify issues and coordinate exchange of scientific information
- n (December) USEPA Draft for Review RfD

1999

- n (February) External peer review of RfD
- n Additional studies completed to fill data gaps in the human health and ecotoxicology database



Timeline

2002

- n USEPA Reassessment. Revised Draft RfD
 - Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization (January 16)
- n External Peer Review Workshop February/March 2002
- n Comments summarized
 - Peer Review of the USEPA’s Draft External Review Document “Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization” (June 2002)
- n USEPA is preparing responses



Timeline

2003

- n (January) USEPA directed to use 1999 interim guidance for perchlorate
- n OW currently monitoring drinking water through the Unregulated Contaminant Monitoring Program
- n U.S. Geological Survey monitoring surface water
- n (June) National Academy of Science (NAS) committee convened to review USEPA's draft RfD
 - Results are due in 15 months

NAS – Overview of Project Scope

- n Assess the effects resulting from ingestion of perchlorate from a clinical, toxicological, medical, and public health perspective
- n Address the following basic science issues
 - Potential adverse effects resulting from disruption of thyroid function at various stages of life
 - Evaluate whether science supports the model that predicts potential adverse neurodevelopmental and neoplastic effects from changes in thyroid hormone regulation resulting from disruption of iodide uptake by the thyroid gland
 - Indicate its level of confidence in the model

NAS – Project Scope

- n Determine levels (degree of confidence) at which chronic inhibition of iodide uptake and changes in thyroid hormones may lead to adverse (not just adaptive) health effects in humans, especially sensitive subpopulations.
- n Consider the influence of iodine in the diet on the levels at which adverse effects would be observed at which adverse effects would be observed.

NAS – Project Scope

- n Evaluate the animal studies used to assess human toxicological effects from ingestion of perchlorate, key endpoints:
 - Changes in brain morphometry, behavior, thyroid hormone levels, and thyroid histopathology
- n Indicate level of confidence in the relevance of the adverse effects observed in the animal studies to human health, especially sensitive subpopulations

NAS – Report

- n Determine whether EPA's findings in its 2002 Draft are consistent with the current scientific evidence.
- n Determine whether EPA considered all relevant literature and used appropriate scientific studies to develop its health risk assessment.
- n Suggest modifications for any deficiencies in the analysis (e.g., lack of consideration of a key study).

NAS – Report

- n Provide a range of values consistent with scientific evidence for percent iodide uptake that would be protective of individuals at various life stages and thyroid status.
- n Provide information that can be used to inform EPA's selection of uncertainty factors used in the approximation of a safe lifetime exposure for humans, especially sensitive subpopulations.
- n Suggest scientific research that could reduce the uncertainty in the current understanding of human health effects associated with low-level perchlorate ingestion.



Perchlorate

ECOLOGICAL HEALTH EFFECTS



U.S. EPA Screening Ecological Risk Assessment – 2002 Draft

Aquatic Toxicity

- n Risk characterization for aquatic life based on Tier II (secondary) aquatic life criteria
- n Not enough data to determine Tier I criteria
- n Secondary acute value = 5 mg/L
- n Secondary chronic value = 0.6 mg/L or 600 µg/L
- n Secondary chronic value determined using an acute-chronic ratio derived from the fathead minnow 7-d data for the sodium salt (NOEC = 208 mg/L)



U.S. EPA Screening Ecological Risk Assessment – 2002 Draft

Aquatic Exposure

- n Large surface water bodies: up to 16 $\mu\text{g/L}$
- n Ground water: up to 280 $\mu\text{g/L}$
- n Near contaminant sources: up to 3,500 $\mu\text{g/L}$

U.S. EPA Screening Ecological Risk Assessment – 2002 Draft

Aquatic Risk Characterization

- n At most sites, the likelihood of effects on the richness and productivity of fish, aquatic invertebrates, and plant communities appears to be low.
- n Where high levels of contamination exist, sensitive aquatic organisms, such as daphnids, may be the most likely to experience effects.

U.S. EPA Screening Ecological Risk Assessment – 2002 Draft

Uncertainties in Aquatic Risk Characterization

- n Spatial and temporal distribution of perchlorate in water is largely unknown
- n Significance of redness and swelling of larvae in the fathead minnow 35-d ELS (early life stage) study (if significant, this could lower the chronic value by over 10-fold)
- n Several key studies had significant limitations (e.g., not conducted to GLP, no analytical measurements)
- n Several recent studies on amphibians were not included because they were not published in time



Recent *Xenopus* (Frog) Studies: Goleman et al., 2002a; 2002b

- n Ammonium salt; 70-d exposures up to 1,175 mg/L
- n No concentration-dependent developmental abnormalities below the 70-d LC50 (223 mg/L)
- n Inhibition of metamorphosis (forelimb emergence, tail resorption, hindlimb growth) occurred in a concentration-dependent manner
- n Tail resorption was inhibited at greater than or equal to 18 µg/L
- n Authors' Conclusion: perchlorate may pose a threat to normal development and growth in natural amphibian populations



Recent *Xenopus* (Frog) Studies: Goleman et al., 2002a; 2002b (con't)

- n Exposures of 59 $\mu\text{g/L}$ and 14.1 mg/L for 70 days
- n Both caused a skewed sex ratio (reduced percentage of males at metamorphosis)
- n Both caused significant enlargement of the thyroid
- n Effects on metamorphosis and thyroid function were reversed during a 28-d non-treatment period

U.S. EPA Screening Ecological Risk Assessment – 2002 Draft

Terrestrial Herbivores

- n Meadow vole (*Microtus pennsylvanicus*)
- n Exposure through water or irrigated/on-site plants
- n Assumed a bioaccumulation factor of 100 from water to plants
- n Screening benchmark = 0.001 mg/kg-day (based on the same rat LOAEL used for assessing human health, with an uncertainty factor of 10 applied)
- n Conclusion: Exposures from both water (surface or ground) and plants will exceed the screening benchmark, sometimes by a significant margin

U.S. EPA Screening Ecological Risk Assessment – 2002 Draft

Uptake in Plants

- n Most data is for woody plants; very limited data for food crops; however additional studies in progress
- n Concentration factors for plants collected at contaminated sites range from 1.5 to 80
- n Uptake and transformation (to chlorite, chlorate, and chloride) has been shown in many species
- n Highest concentrations are generally found in the leaves, followed by stems, then roots



Key Points

- n Recent amphibian data could lower effect levels significantly and have a major impact on the results of the ecological risk assessment
- n Terrestrial wildlife, particularly herbivores, would be at greater risk because of the potential for multi-pathway exposure
- n Could have lower ambient water quality standard than drinking water standard
- n Future crops studies could be significant for human health, as well as, ecological risk assessments