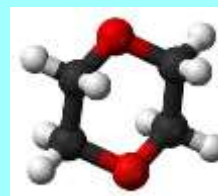


TOXICOLOGY & ENVIRONMENTAL REGULATION OF 1,4-DIOXANE



Dr. Christopher Teaf
*Center for Biomedical & Toxicological Research
Florida State University
Tallahassee, FL*



*Northeast Waste Management Officials Association
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What 1,4-Dioxane Is



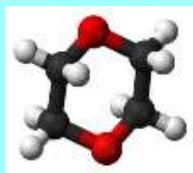
- p-Dioxane; diethylene dioxide; CAS 123-91-1
- Receiving a great deal of attention in last 10-15 years
- Clear liquid with faint “pleasant” or “sweet” odor
- Historical solvent stabilizer, ethoxylation byproduct
- Paint strippers, dyes, greases, varnishes, waxes
- Cosmetics
- Laboratory component (liquid scintillation counter fluids)



More About 1,4-Dioxane

- In manufactured food additives and food packaging materials
- Food crops treated w/pesticides containing 1,4-dioxane
- Detergents
- Johnson & Johnson Safety and Care Commitment
- Tide detergent, 2013 CA Proposition 65 decision and resultant <25 ppm commitment by P&G

1,4-Dioxane Phys/Chem Properties



- Flammable at high levels in air
- Low HLC
- Miscible in water
- Highly mobile
- Recalcitrant to bacterial degradation, conventional air stripping
- Leaching potential to groundwater high

WHAT HAPPENS TO 1,4-DIOXANE when it's released to...

Air

- Evaporates, VP 38 mmHg @ 25°C
- Degrades to form aldehydes, ketones



Soil

- Tends to migrate through soil, not adsorb to particles (exc. moist clay/silt)



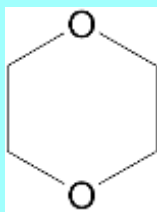
WHAT HAPPENS TO 1,4-DIOXANE when it's released to...

Water

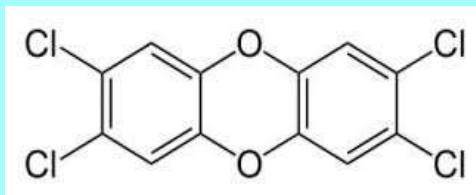


- Miscible in water, travels ahead of other solvents in plume (like MTBE)
- Stays dissolved, low volatility from GW, SW
- Chemically stable, does not readily degrade in GW or SW

One Thing That it Isn't ...

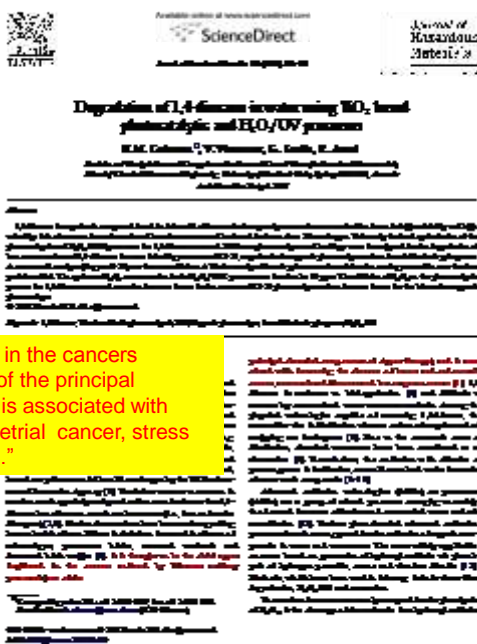


- 1,4-dioxane
- $C_4H_8O_2$
- MW = 88 g/mole
- HLC = $4.9E-06 \text{ atm}\cdot\text{m}^3\cdot\text{mol}^{-1}$
- CSF = $0.11 \text{ (mg/kg}\cdot\text{day)}^{-1}$



- 2,3,7,8-TCDD ("dioxin")
- $C_{12}H_4Cl_4O_2$
- MW = 322 g/mole
- HLC = $1.6E-05 \text{ atm}\cdot\text{m}^3\cdot\text{mol}^{-1}$
- CSF = $1.5E+05 \text{ (mg/kg}\cdot\text{day)}^{-1}$

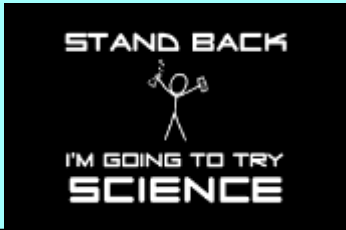
Just When You Think It's Too Obvious ...



"It is thought to be the chief agent implicated in the cancers suffered by Vietnam military personnel (one of the principal chemical components of Agent Orange) and is associated with increasing the chances of breast and endometrial cancer, stress related disorders and lower sperm counts [5]."

Scientific Truisms

- You will never see something you are not capable of finding
- It is difficult to find something if you are not looking for it
- You cannot evaluate something without quantitative information
- Risk evaluation requires knowing what and how much is where
- New things are being learned all the time



Analytical Methods

- Require separation from water of very hydrophilic substance
- Historical methods used 8260B, 8261, 8270D, 524.2
- Selective Ion Monitoring (SIM)
- EPA developed 522 in 2008, common now
- Seeking low detection limits (sub ppb)
- Different sample preparation
- “Dirty” samples can be problematic
- More detail in later presentations



Toxicology of 1,4-Dioxane - I

- Greatest exposure potential – ingestion
- Eye, respiratory tract irritant at high concentrations ($>400 \text{ mg/m}^3$)
- Not acutely toxic (oral LD_{50} about $\frac{1}{2}$ that of table salt)
- Liver and kidney toxicity at high exposure levels
- Not bioaccumulative



Toxicology of 1,4-Dioxane - II

- Carcinogenic potential in animal studies only
 - ✓ nongenotoxic or only weakly genotoxic
 - ✓ based on tumors of liver, nasal squamous cells
 - ✓ predictive value of existing data uncertain
- Limited, inconclusive human data (1970s)
- Evidence good for hyperplasia, cell proliferation, promotion
- Toxicity-based soil, GW criteria highly restrictive



Proposed Mechanism of Action (MOA)

- Dourson et al., 2014 - tumors follow cytotoxicity
- Negative *in vitro* mutagenic results
- USEPA – concluded in 2013 that present data insufficient, but concur on promotion rather than initiation ... big risk difference
- Chloroform analogy (*MCLG 70 ug/L vs 0.22 ug/L RSL*)
- More studies to come – stay tuned, may affect future guidance
- Compare sub-ppb vs 350 ppb health-based target



Dourson et al. (2014)

- Regulatory Toxicology & Pharmacology 68: 387-401
- Reevaluation of 1978 NCI histopathology for mice re: liver tumors, inconsistent with recent studies (e.g., Kano et al., 2008)
- Identified clear dose-related, non-neoplastic cytotoxicity
- hypertrophic hepatocyte response, followed by necrosis, inflammation, hyperplastic hepatocellular foci
- Mutagenicity “credibly excluded”
- Reference Dose (RfD) of 0.05 mg/kg•day proposed
- Yields 350 ppb as health-based GW goal (including 20% RSC)

Regulatory Status: Evolving

- 1981 NTP Reasonably Anticipated Human Carcinogen
- 1988 EPA Group B2 Probable Human Carcinogen (*CSF 0.011 (mg/kg•day)⁻¹*)
- 1990s ACGIH A3; IARC Group 2B
- 2001 Mohr White Paper (Santa Clara Water District); also 2010 book
- 2005 EPA - Likely to be carcinogenic to humans; WHO guideline 50 ug/L
- 2010 Revised CSF 0.11 (mg/kg•day)⁻¹
- 2012 EPA Health Advisory Level 0.35 ug/L (35 ug/L)
- 2013 Revisions to USEPA Tox Review (Inh)
- 2015 No MCL; DWEL 1 mg/L; Tap RSL 0.46 ug/L
- 2015 EPA TSCA Workplan Issued (April)



Other Agencies

- **USFDA**
 - ✓ 10 ppm limit in N-9 contraceptive sponge spermicide
 - ✓ 10 ppm limit in glycerides and polyglycerides (supplements)
 - ✓ Levels observed in cosmetics do not pose a hazard
- **NAS**
 - ✓ 10 ppm limit in polysorbate, a food additive
- **Occupational Guidelines**
 - ✓ OSHA - 100 ppm limit in occupational air (360 mg/m³)
 - ✓ ACGIH - 20 ppm limit in occupational air (72 mg/m³)

State Criteria – Highly Variable

- CA “Safe Harbor” cosmetics limit 30 ug/day (NOEL)
- CO Interim GW Standard 6.1 → 3.2 → 0.35 ug/L
- FL Groundwater target 3.2 ug/L; proposed 0.4 ug/L 2015
- MN 1 ug/L drinking water
- MI Risk-based screening level of 85 ppb in GW
- More on NE criteria in later presentations



International Guideline Levels

- Where does EPA stand? ... good question
 - ✓ *0.46 ug/L RSL presently (June, 2015)*
 - ✓ *2013 value of 0.67 ug/L, early 2015 value of 0.78 ug/L due to differences in exposure assumptions*
 - ✓ *Health Advisory Levels – 0.35 ug/L to 35 ug/L (2015 IRIS)*
- WHO - Drinking Water Guideline – 50 ug/L
- Canada, Australia – no drinking water guideline



Soil Concentration Guidelines

- Direct contact
- Protection of groundwater
- EPA RSL (residential direct contact) – 5.3 mg/kg
- EPA RSL (industrial direct contact) - 24 mg/kg
- EPA RSL (groundwater protection) – 9.4×10^{-5} mg/kg (94 ppt)
- State residential direct contact - range from 0.2 to over 500 mg/kg
- State protection of groundwater – 0.00016 to 1.7 mg/kg
- More detail in later presentations



Selected Reference Documents

- EPA (2015) TSCA Problem Formulation, Initial Assessment
- ATSDR (2012) Toxicological Profile for 1,4-Dioxane
- CO DPHE (2012) Notice of Public Rulemaking Hearing
- EPA (2012) Drinking Water Standards & Health Advisories
- EPA (2010, 2013) Integrated Risk Information System (IRIS)
- Mohr (2010) Environmental Investigation and Remediation: 1,4-Dioxane and Other Solvent Stabilizers
- EPA (2006) Treatment Technologies for 1,4-Dioxane: Fundamentals and Field Applications

Treatment Possibilities

- Variably effective
 - Air sparging
 - Soil vapor extraction (SVE)
 - Bioremediation
- Effective
 - Advanced Oxidation Processes (AOP)
- Innovative, mixed reviews
 - Phytoremediation
 - Electrical Resistance Heating (ERH)
- More detail in later presentations



Conclusions

- 1,4-dioxane has “emerged” at some impacted sites
- BDL is often a worthy goal ... but how useful is that conclusion?
- Recent evidence that 1,4-dioxane causes tumors only at doses capable of causing cytotoxicity; would change tox landscape
- Conflicts and challenges exist regarding health-based targets and available analytical / engineering options
- 1,4-dioxane detection can greatly increase costs, extend cleanup activities, though human health risks are highly uncertain
- Stay tuned



Questions or Comments?

Dr. Christopher Teaf
cteaf@hswmr.com
(850) 681-6894