C8: History, Background, and Risk Assessment

Susan Goldhaber
Hazardous Waste Section
North Carolina Dept. of Environment and Natural Resources
What is C8?

- Perfluorooctanoic Acid (PFOA)
- $\text{C}_8\text{H}_2\text{F}_{15}\text{O}_2$
- Ammonium Perfluorooctanate (APFO) is one of its salts – form most often used in industry and form most tested in animal studies
- Once in the body, PFOA disassociates to APFO
What is C8 (continued)

• One of many perfluorinated compounds, known as perfluorochemicals (PFCs)
• Fluorine atoms completely replace the hydrogen atoms typically attached to organic hydrocarbon molecules
• High strength of carbon-fluorine bond: stable, nonreactive, and resistant to degradation
• Perfluorooctyl sulfonate (PFOS) (another PFC that is known to be an environmental contaminant and present in human blood)
Production of PfCs began in 1947

Major use as a processing agent for products that resist heat, oil, stains, and grease

Common uses: production of nonstick cookware (Teflon), Scotch-gard, and firefighting foams
C8 Production

• C8 produced:
  • By 3M in Cottage Grove, MN from late ‘40s - 2002
  • By DuPont near Parkersburg, WV from late ’40s – 2003
  • By DuPont near Fayetteville, NC from 2002 - present
  • DuPont (Fayetteville, NC) only facility producing C8 in the U.S. today
History: Environmental Problems

- 2001 – Class action lawsuit filed by OH and WV residents - drinking water contamination by C8
- Late 2001 - Consent order between DuPont and WV, established 2 scientific teams: 1) conc. C8 in groundwater, 2) toxicity C8 and screening levels
History (continued)

• March, 2002 – EPA Regions 3 & 5 signed consent order with DuPont, alternative water supplied to any resident in OH or WV with C8 in water > 14 ppb
• 2003 – Petition from EWG to EPA to investigate DuPont violating TSCA 8(e) (developmental effects in animals)
• December, 2004 – MOU between EPA and 3M & Dyneon on monitoring for C8 in AL
• November, 2005 – MOU between EPA and DuPont on monitoring for C8 in WV
• December, 2005 – DuPont agreed to pay $10.25 million in civil fines and $6.25 to fund research projects
History (continued)

• January, 2006: EPA global stewardship program on C8 and other PFCs. 8 U.S. companies asked to reduce C8 emissions by 95% by 2010 and eliminate C8 from emissions and product content by 2015. (DuPont and others have agreed)

• March, 2006: EPA proposed to exclude C8 and other PFCs from being exempted from TSCA PMN requirements (polymer exemption rule); would be required to notify EPA before manufacture or importing chemical
EPA Risk Assessment

• January, 2005, “Draft Risk Assessment of the Potential Health Effects Associated with Exposure to Perfluorooctanoic Acid and its Salts” issued by OPPT
EPA Risk Assessment (continued)

- Summary of epidemiology studies (worker studies)
- Summary of toxicity studies in animals
- Weight of evidence for carcinogenicity
- Margin of exposure (MOE) estimates
- **No** RfDs, RfCs, or cancer risk estimates calculated
EPA Risk Assessment: Toxicity Studies

- Crosses placenta in rats
- Liver is the primary target organ
- Adult male rats showed effects at lower doses than female rats
- Immunotoxic in mice
- Reproductive effects in rats
- Not mutagenic in variety of tests
EPA Risk Assessment: Carcinogenicity

- Epidemiology studies:
- All on workers, only 1 study stat. sig. positive results - prostate cancer. Update to study - negative.
EPA Risk Assessment: Carcinogenicity

• Animal studies:
• 2 dietary (2-year) studies in rats:
• First study: Significant increase in testicular (Leydig) cell adenomas in males & mammary fibroadenomas in females
• Second study: Significant increase in Leydig cell adenomas, liver adenomas, & pancreatic acinar cell tumors
EPA Risk Assessment – Carcinogenicity

- Conclusion: 2 carcinogenicity studies showed C8 caused liver, Leydig cell, and pancreatic tumors in rats; evidence for mammary tumors equivocal because incidences comparable to historical controls.

- C8 exhibited “suggestive” evidence of carcinogenicity but not sufficient to assess carcinogenic potential.
EPA Risk Assessment: Carcinogenicity

• Basis for EPA’s “suggestive” evidence of carcinogenicity:
  • Liver tumors probably due to PPARα-agonist mode of action: not relevant to humans
  • Absence of liver cell proliferation in 6 month study in monkeys
  • Absence of carcinogenic effects in human studies
  • Leydig cell & pancreatic tumors probably not relevant to humans (hormone & toxicodynamic differences)
  • Mammary tumors equivocal based on comparison with historical control group
EPA Risk Assessment: Carcinogenicity

• SAB draft report reviewing C8 risk assessment issued January 20, 2006
• Concluded that carcinogenicity stronger than proposed by EPA – should be considered “likely to be carcinogenic in humans.”
EPA Risk Assessment: Carcinogenicity

• Basis for the SAB’s “likely to be carcinogenic in humans”:
  • 2 feeding studies show cancer in animals
  • Uncertainties over whether PPARα-agonist is the only mechanism for C8 effects on the liver
  • Inappropriate to exclude mammary tumors, comparing to the concurrent control group showed increase in tumors
  • Insufficient evidence for mode of action for Leydig cell, pancreatic cell, and mammary tumors, so must be presumed relevant to humans.
EPA Risk Assessment: Carcinogenicity

- A few SAB panel members disagreed with carcinogenicity conclusions
- Evidence more consistent with EPA’s “suggestive evidence” of carcinogenicity
- Basis: 1) PPARα-agonist probably sole mode of action for liver tumors, 2) mammary tumors not significant since no increase in animals compared to historical controls
EPA Risk Assessment: Margin of Exposure Analysis

• MOE = ratio of NOAEL or LOAEL to estimated human exposure level

• Compared internal doses from animal and human biomonitoring studies, instead of external exposure estimates (traditional method)

• MOEs calculated:
  • Adults: 16,739 (based on monkey study); 9,158 for males, 398 for females (based on rat study)
  • Developmental effects: Prenatal period: 823 or 3,095; Postweaning period: 10,484 – 78,546 (based on rat study)
Other Risk Assessments

• West Virginia C8 Assessment of Toxicity Team (CATT) Report issued in August, 2002

• Report result of Consent Order between DuPont and WV

• Calculated RfD of 0.004 mg/kg-day

• Calculated water screening level (SL) of 150 µg/L, air SL of 0.1–6.0 µg/m³, soil SL of 240 mg/kg
State guidance levels for C8

- North Carolina: 2 µg/L in water, RfD = 0.0003 mg/kg-day (based on 2-generation reproductive study in rats)
- West Virginia: 150 µg/L in water; RfD = 0.004 mg/kg-day (based on same 2-generation reproductive study in rats)
- Minnesota: 7 µg/L in water; RfD = 0.001 mg/kg-day (based on 26 wk study in monkeys)
- Ohio: Using West Virginia’s numbers
- New Jersey: 5 µg/L in water (based on default level for compounds having “evidence of carcinogenicity”)
C8 in Humans

- Detected in blood in people across the U.S.
- Studies on 3 separate age groups: mean C8 levels of 4-5 ppb in blood
C8 in the Environment

- Detected in the Great Lakes: 27-50 ng/L
- Most rivers and lakes in Japan: 2-10 ng/L
- Sediment in U.S. & other countries: (24 pg/g-18 ng/g)
- Precipitation in U.S. (<10 ng/L-50 ng/L)
- Snow and ice caps in Arctic (2-3 ng/L)
Summary

- C8 found throughout the environment at ng/L levels
- Also detected in human blood at average levels of 4-5 ppb
- Epidemiology studies and MOE analysis have not shown cause for concern
- Carcinogenic effects seen in animal studies require further study but also show importance of limiting exposure to compound