Dow Epidemiology Studies
Among Workers with Exposure to Dioxins and Dioxin-like Compounds

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Outline
- Chemistry
- Toxicology
- Sources of Exposure
- Dow Worker Studies
- Well Known Dioxin Exposure Studies
- Summary

What are dioxins & dioxin-like compounds?
- Diverse range of chemical compounds which are known to exhibit “dioxin-like” toxicity
  - Dioxins
  - Furans
  - PCBs
- Most toxic dioxin in the class is thought to be 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
- Trace amounts of dioxins are generated during the combustion process with the current leading sources being backyard trash burning, forest fires and it can also be generated in chemical processes such as paper pulp bleaching and herbicide manufacturing.
Dioxins

2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD)

- 75 congeners, but only 7 dioxins are thought to be toxic and found in the body
- Furans and PCBs (similar to dioxins) are also present in the body
- Dioxins, furans and PCBs summed to produce toxic equivalents (TEQs) based on animal data & ranked relative to TCDD

Trichlorophenol Dioxin Profile

2,4,5-Trichlorophenol  2,3,7,8-TCDD

Pentachlorophenol Dioxin Profile

Octachlorodibenzo-dioxin
Heptachlorodibenzo-dioxin
Hexachlorodibenzo-dioxin
(1,2,3,4,7,8), (1,2,3,6,7,8), and (1,2,3,7,8,9) Isomers
Toxicology: Animal Studies

- Some animal species are acutely sensitive to 2,3,7,8-TCDD
  - Non-lethal levels in food can cause a variety of adverse effects: weight loss, biochemical & degenerative changes in the liver, hair loss, swelling of the face, & moderate to severe chloracne.
- Humans less susceptible to 2,3,7,8-TCDD than many animal species

Summary of Dioxin Literature: Potential Human Health Effects of Dioxins

- Wide range of scientific opinion on dioxins based on numerous animal and human studies
- Increased risk of chloracne among persons with high exposure
- Acute liver effects with high exposure
- No consistent findings across studies of increased site specific cancer risks among humans at high exposure levels
  - While some studies show increased risk of all cancers combined, we feel this finding is not biologically plausible
- Insufficient human evidence of a causal association for other health outcomes

U of M Study: How are people exposed to dioxins?

- Well designed
- Largest study done on environmental exposure
- All routes of exposure examined
- Areas above background in soil & sediments
  - According to US EPA, primary route of exposure is through food, not soil or air (98%).
- No correlation between body burden & dioxin soil levels for past 30 yrs
- Slightly higher body levels of dioxins in people who lived in the Midland area prior to 1980
- Age, amount of body fat, smoking also related to dioxin body levels
Famous Dioxin Exposure

Viktor Yuschenko

- Former President of Ukraine
- In September 2004 he fell ill just weeks before the presidential election after a dinner with political foes
- Severe abdominal pain and lesions on his face, shoulders, chest, back and abdomen. His liver, pancreas and intestines were edematous, with ulcers covering his digestive tract.
- British toxicologist suggested symptoms consistent with dioxin exposure
- Tests revealed TCDD ~ 50,000× background levels; very pure – suggests synthesized in a lab

Chloracne: Typical Setting

Seen in workers in contact with halogenated aromatic compounds: chemical manufacturing workers, laboratory workers, maintenance workers, waste handling workers, workers in different industries using certain halogenated hydrocarbons

- Chloronaphthalenes
- Polychlorinated biphenyls (PCBs)
- Polychlorinated dibenzo-p-dioxins (PCDDs)
- Polychlorinated dibenzofurans (PCDFs)

Chloracne: lesions mainly on face; also chest, back & abdomen
Chloracne

- Acute acne-like skin disorder caused by high exposure to chlorinated hydrocarbons
  - **Mild cases**: Blackheads may be limited to the area around the eyes, extending along the temples to the ears.
  - **More severe cases**: Blackheads also may appear in other places, especially over the cheek bone area, other facial areas, behind the ears, along the arms, shoulders, chest, back, and abdomen.
- Severe chloracne may lead to open sores and permanent scars.
- Skin may become thicker and flake or peel.
- While all cases eventually resolve, the minor cases resolve more quickly.
- Route of exposure: Direct skin contact most common, but ingestion and inhalation may also be a factor.
- Can develop from three to four weeks after exposure.

**Treatment of Chloracne**

- **Olestra**: A fat substitute that adds no fat, calories, or cholesterol to products.
  - Was used in the preparation of traditionally high-fat foods such as potato chips.
  - In the late 1990s, Olestra became infamous in American popular culture for its unpleasant side effects.
  - Draws fat out of the body as well as fat-solubles (e.g., some vitamins and dioxins).

**Dow Studies on Health Effects after Dioxin Exposure**

- We have a long history of studying health effects among our workers including those exposed to dioxins.
- We have published the results of many studies on the health effects of dioxins:
  - Examining cancer, diabetes, heart disease, chloracne, spontaneous abortions, stillbirths, infant deaths, malformations, number of conceptions, high blood pressure, liver trouble, kidney trouble, bladder trouble, ulcers, and hematology.
- Other than chloracne, we have seen no indication of increased risk of health effects in our workers related to dioxin exposures.
Summary of Dow Midland Study

- The largest of the industrial studies of dioxin exposures at a single location
  - Most workers at a single plant (2,192)
  - Longest follow-up (1940-1994)
- Exposures validated by over 400 serum dioxin evaluations
- We continue to follow the cause specific mortality of these workers
**Health Effects Studied**

- **Causes of death**
  - Cancer (Lung, soft tissue sarcoma, non-Hodgkin lymphoma)
  - Heart disease
  - Diabetes
- **Male-mediated reproductive effects**
- **Medical surveillance**
- **Diagnoses for chronic conditions**
Relative Risk & 95% Confidence Interval of Cancer Among Dow’s Pentachlorophenol Workers using IARC Cancers of Concern

Source: Collins et al. 2009

Summary of New Zealand Study

- Study done at Otago University in 2007
- TCP process closed down in 1988
- About 900 workers with potential exposure
  - Followed-up since 1969
- Serum blood dioxin levels indicated significant exposures among dioxin workers

Relative Risk & 95% Confidence Interval of Cancer Among Dow’s Pentachlorophenol Workers

Source: Collins et al. 2009

Relative Risk & 95% Confidence Interval of Cancer in New Zealand Trichlorophenol Workers

Source: McBride et al., 2007
Male-Mediated Reproductive Outcomes

- Study conducted in 1980
- Study Design
  - Examine reproductive outcomes of spouses of workers exposed to dioxins
  - Questionnaire administered to
    - 370 spouses of husbands exposed
    - 345 spouses of husbands not exposed

Relative Risk & 95% Confidence Interval of Male-mediated Reproductive Effects

Study of Medical Surveillance and Chronic Disease Diagnoses

- Study conducted in 1981
- Study population
  - 204 men working 2,4,5-T operations 1950-71
  - 61 men with chloracne from a 1964 incident
  - Referents include other workers at site not exposed

- Outcome information
  - Dow’s medical surveillance examination
    - Laboratory tests
  - Diagnoses from external medical service providers from group insurance
Only finding in the study was more x-ray confirmed ulcers among workers in low exposed dioxin group. Workers with higher dioxin exposures did not have increased risk of this outcome. No other differences between groups on other chronic conditions.

Dow Worker Study Conclusions

- Our studies have been extensively reviewed and communicated peer reviewed journals
- Dioxin exposures among Dow Chlorophenol workers were above background
- Other than the presence of chloracne, no other health effects have been observed
- We find no evidence of increased cancer rates in our chlorophenol workers
- Our findings are consistent with other studies of highly exposed persons
Other Studies of Dioxin Exposures

Several other groups of workers with high dioxin exposures have been studied.

Cancer Rates for Selective Citation of Dioxin Literature

Kogevinas et al., AJE, 1997 (20 or more exposure years)
Consonni et al., AJE 2008 (Zones A and B)

Well Known Dioxin-like Exposure Studies

- Chloracne Industrial Studies – 1940’s Nitro, WV & 1960’s Midland, MI
- Ranch Hands Study – 1965 Defoliant Application
- Seveso Italy 1976 Plant release
- Rice Oil Poisonings China & Japan ad year
- PCBs in Anniston, Alabama
Summary

When we learned about the affects of exposure to dioxins 40 years ago, we took steps to minimize exposure to our workers and limit releases to practically zero.

- TCDD is clearly toxic & carcinogenic to animals
- TCDD toxicity varies greatly among species
- Toxicity of other dioxins is less certain as acknowledge by EPA
- Abundant human data indicates limited evidence of carcinogenicity
- Extrapolation of animal data and human data at high exposure levels to lower environmental levels is fraught with uncertainty

Questions???