

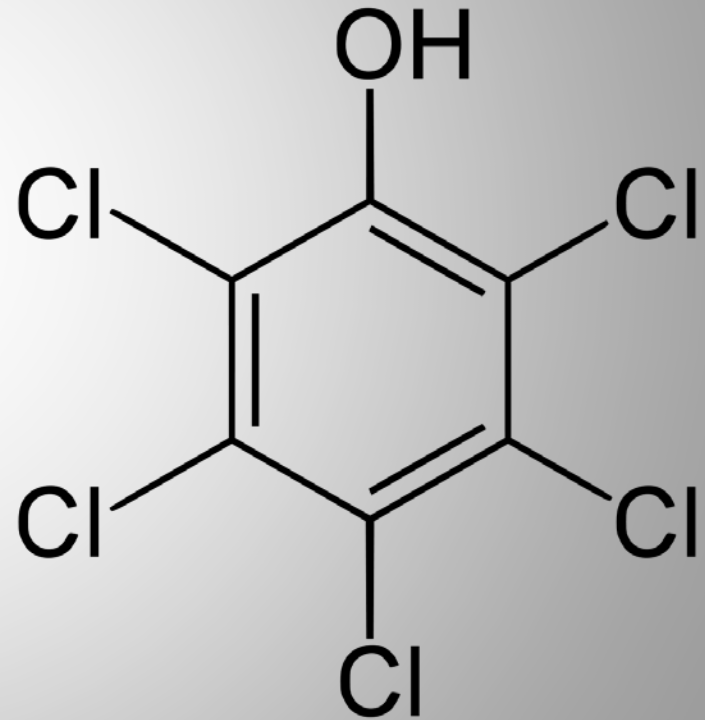
Occupational Studies of Workers in Pentachlorophenol Production

James J. Collins, PhD

The Dow Chemical Company

Published Epidemiology Studies of Workers Manufacturing Pentachlorophenol

- Dow (Midland, Michigan)
 - Collins et al. 2007; Ramlow et al. 1996
 - Ruder & Lin 2011
- Middle Volga Chemical (Chapaevsk, Russia)
 - Revich et al., 2001
- Monsanto (Krummerich in Sauget, Illinois)
 - Hryhorczuk et al. 1998
 - O'Malley et al. 1990
 - Ruder & Lin 2011
- Monsanto (Newport, South Wales)
 - Baxter, 1984
- Phillips (Amsterdam, The Netherlands)
 - Boers et al. 2010; Bueno de Mesquita et al. 1993
- Reichhold (Tacoma, Washington)
 - Ruder & Lin 2011
- Spolana (Czech Republic)
 - Jirasek et al. 1976
- Tianjin Chemical (Tianjin, China)
 - Cheng et al. 1993
- Vulcan (Wichita, Kansas)
 - Ruder & Lin 2011

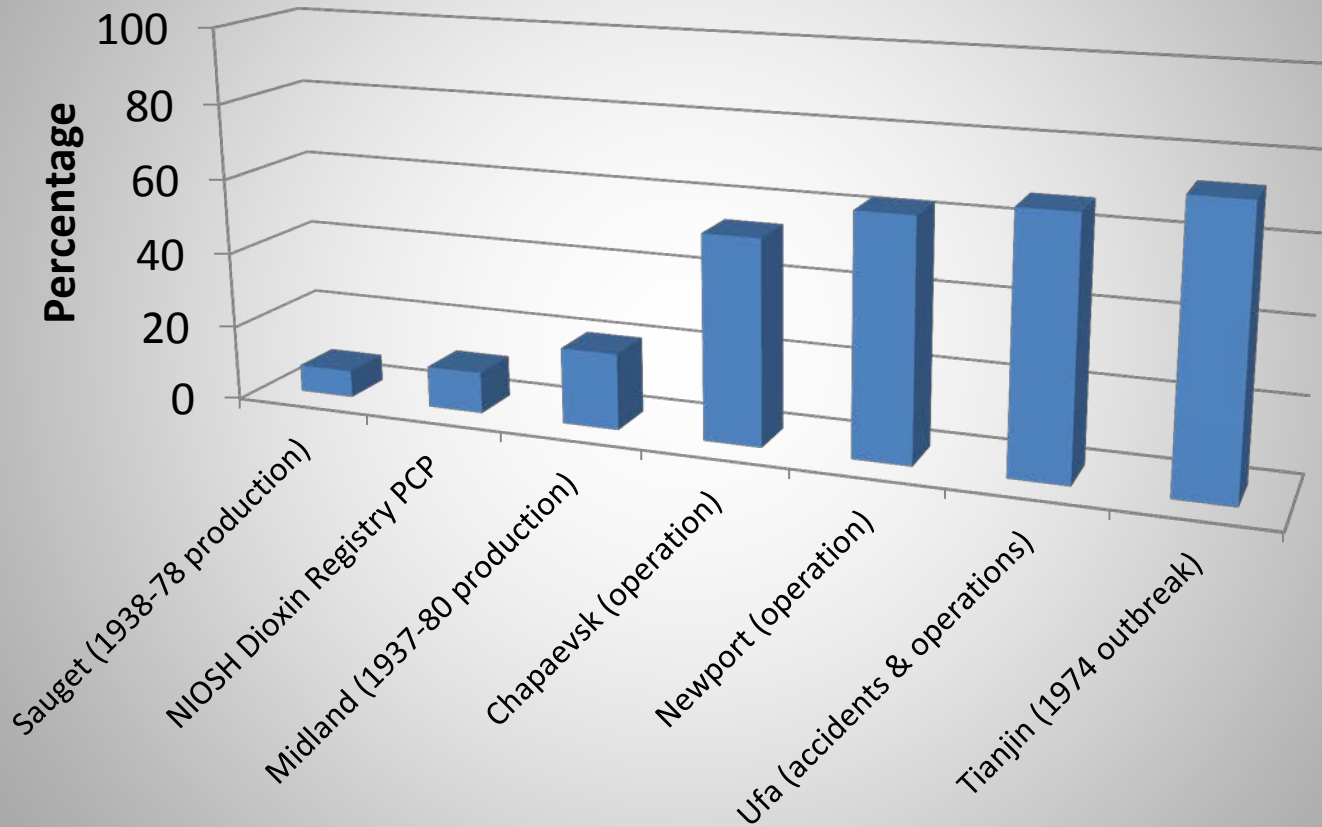


Exposures in PCP Manufacture

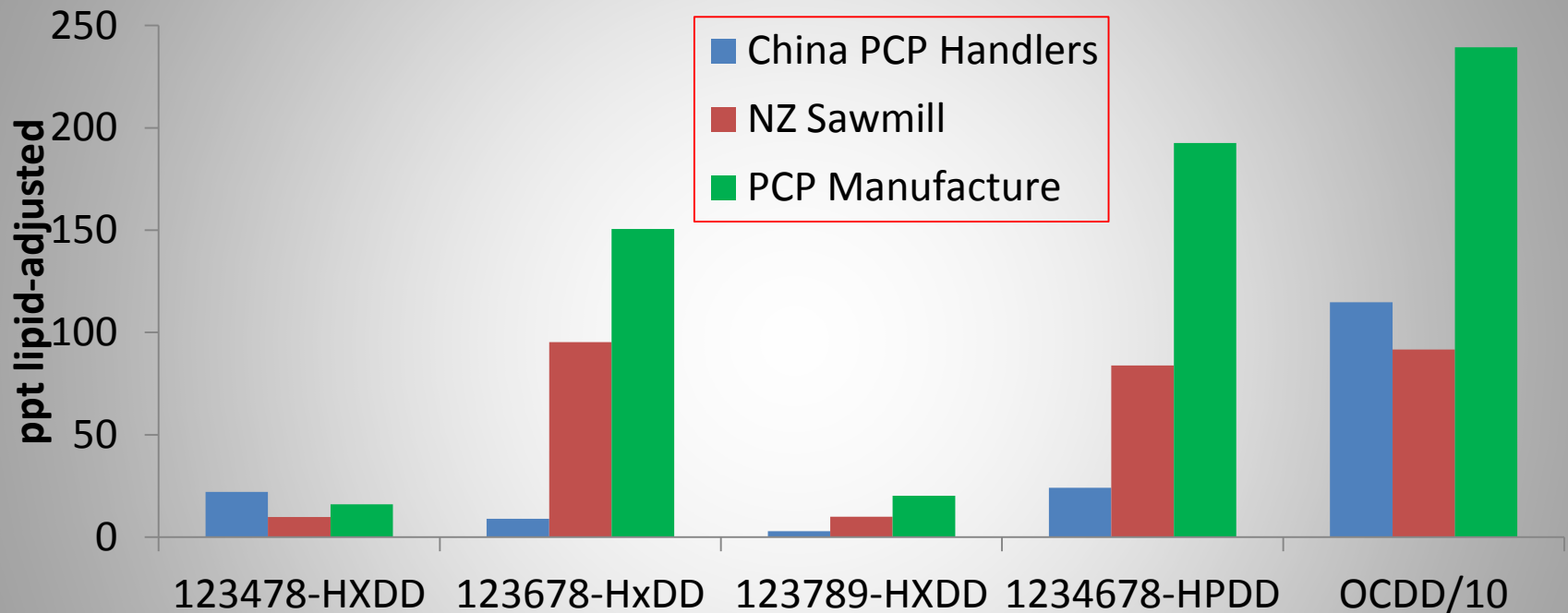
- Exposures thought to be highest in PCP manufacture compared to wood treating, pulp & paper, and sawmill
 - Most cases of chloracne reported in PCP manufacture
 - Supported by Limited serum dioxin evaluations
- Chloracne has rarely occurred in wood treating industry
 - Case study (Cole et al. 1986)
 - Dermal exposure from poor work practices
- Case control studies have relatively low dioxin levels and often no difference in dioxin levels between cases and controls (Hardell et al., 2001)

Sources: Williams 1982; Schechter et al. 1994; Collins et al. 2007; McLean et al. 2009

Percentage of PCP Manufacturing Workers Who Developed Chloracne



Lipid adjusted serum dioxin and furan levels



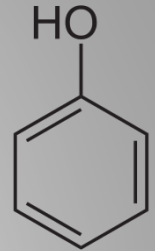
Source: Schechter et al. 1994; Collins et al. 2007; McLean et al. 2009

Thursday, April 10, 2013

Two Methods of Making PCP

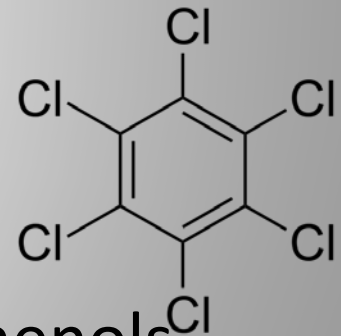
1. Chlorination of phenol

- a. Mostly widely used (all US production)
- b. Contaminants include polychlorinated phenols (tetra-, tri-), hexachlorobenzene, dioxins (HXDD, HPDD, OCDD), and some furans



2. Hydrolysis of hexachlorobenzene

- a. Used sometimes in Europe and China
- b. Contaminants include polychlorinated phenols (tetra-, tri-), hexachlorobenzene, dioxins (TCDD, HXDD, HPDD, OCDD), and some furans



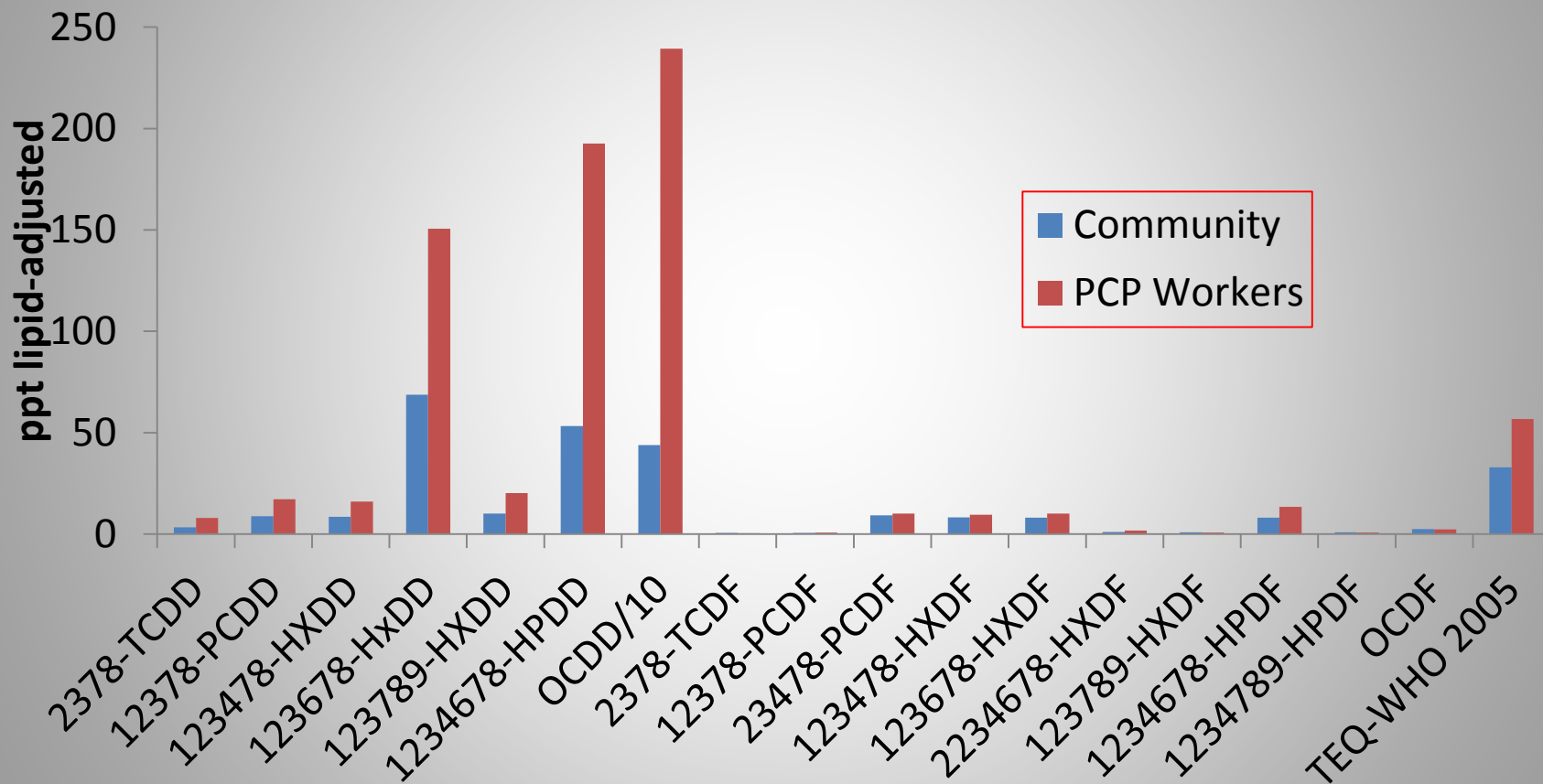
Estimated Half-Life in Human Body

Substance	Half-life
Pentachlorophenol	30-50 hours
Tetrachlorophenol	30-50 hours
Trichlorophenol	30-50 hours
Hexachlorobenzene	2.5-3.0 years
2378-TCDD	6.5 years
123478-HXDD	7.0 years
123678-HxDD	9.0 years
123789-HXDD	6.3 years
1234678-HPDD	6.7 years
OCDD	7.3 years

Sources: Plimmer 1973; ATSDR 2001; Aylward et al. 2013

Thursday, April 10, 2015

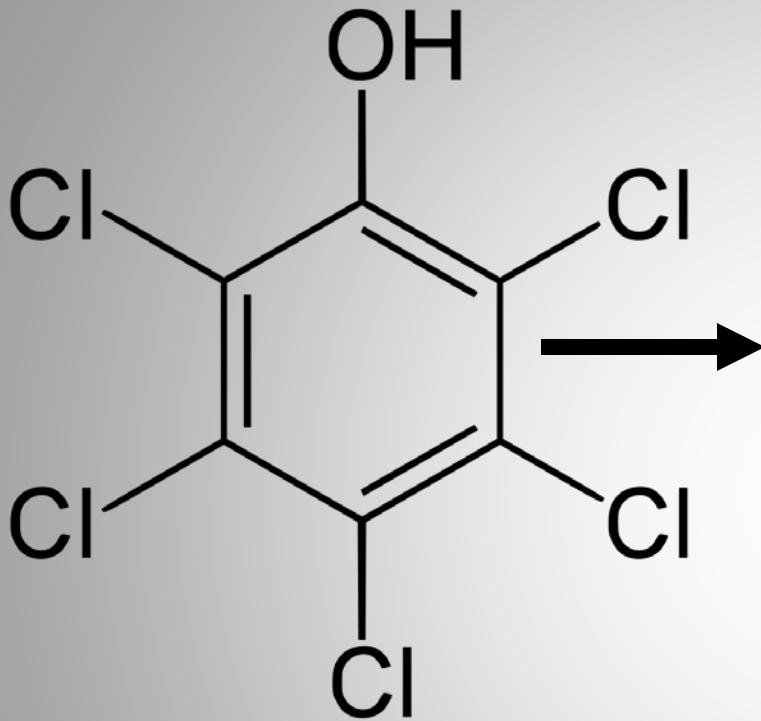
Lipid adjusted serum dioxin and furan levels



Source: Collins et al. 2007

Thursday, April 10, 2013

US Pentachlorophenol Dioxin Profile



Octachlorodibenzodioxin

Heptachlorodibenzodioxin

**Hexachlorodibenzodioxin
(1,2,3,4,7,8), (1,2,3,6,7,8),
and (1,2,3,7,8,9) Isomers**

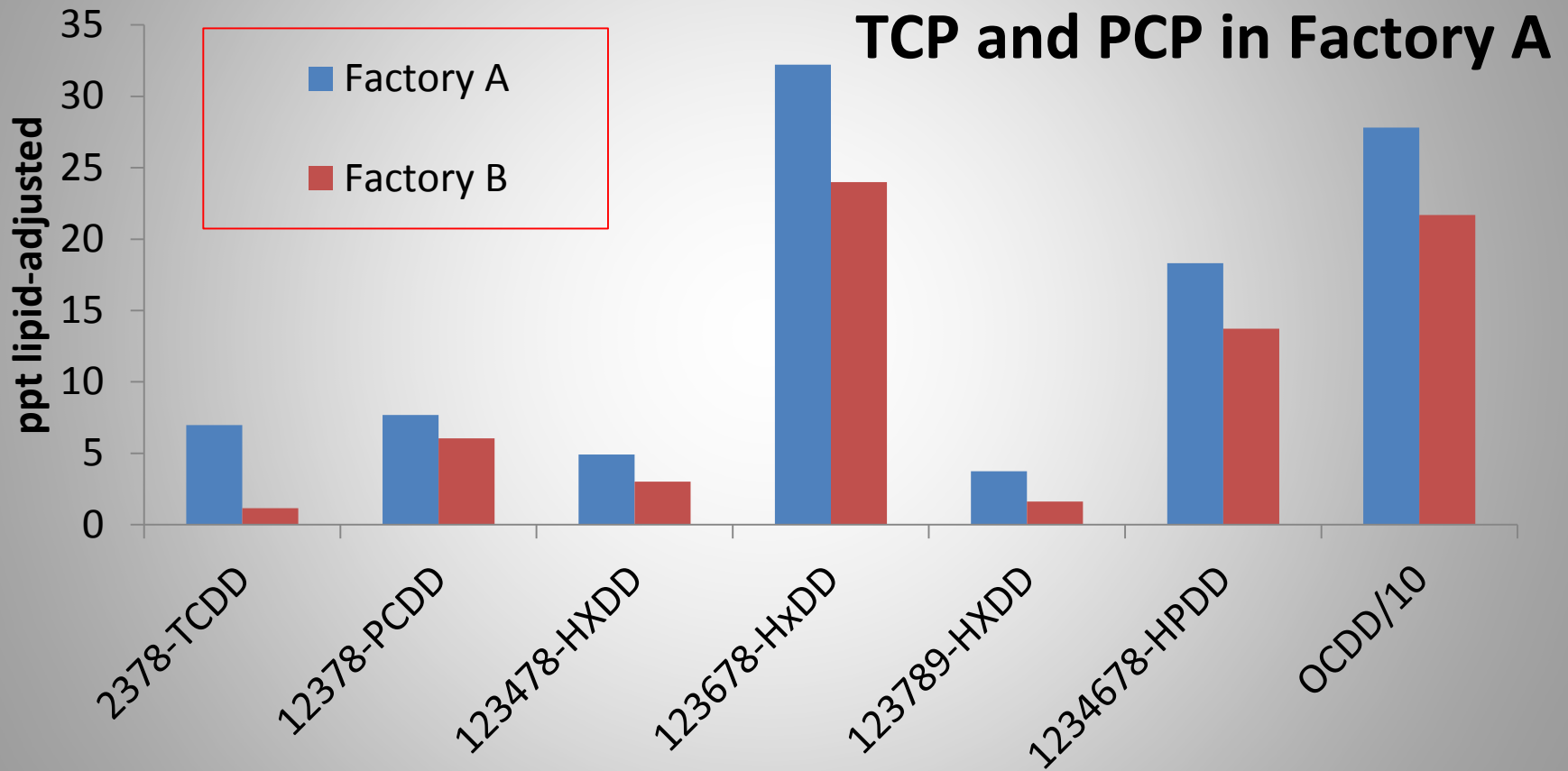
Biomonitoring

- Chlorophenols disappear rapidly in the body
 - difficult to access past exposure from biomonitoring
- Dioxins are long-lived in the body
 - could be used as indicators of past exposure to not only dioxins, but also to commercial PCP
 - assumes level of contaminants constant

Other Exposures

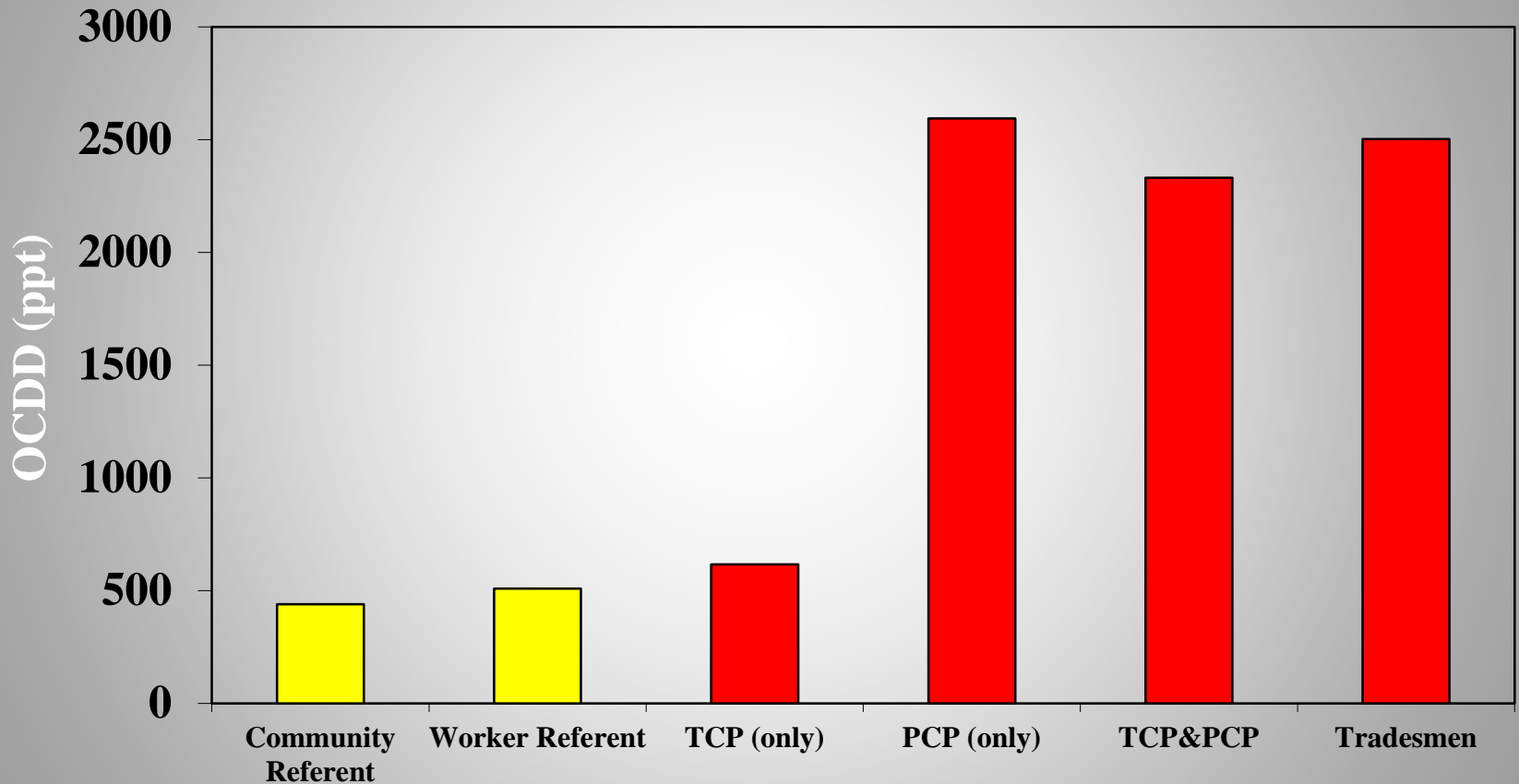
- PCP was often made in plants making other pesticides including 2,4,5 trichlorophenol (TCP) and 2,4,5 trichlorophenoxyacetic acid (2,4,5-T)
- Many other potential exposures depending on site

Lipid adjusted serum dioxin levels



Source: de Mesquita et al. 1993; Boers et al., 2010

OCDD Levels



Source: Collins et al., 2007

Thursday, April 10, 2013

Treatment of Mixtures

- Occupational exposures are always mixtures of exposures
- Approaches for mixtures in epidemiology
 1. Independent – each exposure produces separate exposure response
 - Focus on one chemical and ignore others (most common)
 2. Additive – two or more chemicals have additive effect on exposure response
 - TEQ for dioxins
 3. Synergistic – total effect is greater than the sum of the effects
 - Smoking, asbestos and lung cancer
 - Smoking, arsenic and lung cancer
 4. Antagonist – Some chemicals interfere with the toxic impact of other chemicals
 - Selenium and mercury in diet

Methods of Exposure Assessment

1. Four dimensions of exposure

a. Identity

- PCP and contaminants
 - Dioxin's Toxic Equivalents

b. Form

- Distilled, solution (oil or aqueous), flakes, prills, blocks
 - Dermal, inhaled, ingested

c. Concentration

- Expert opinion
- Industrial hygiene monitoring
- biomonitoring

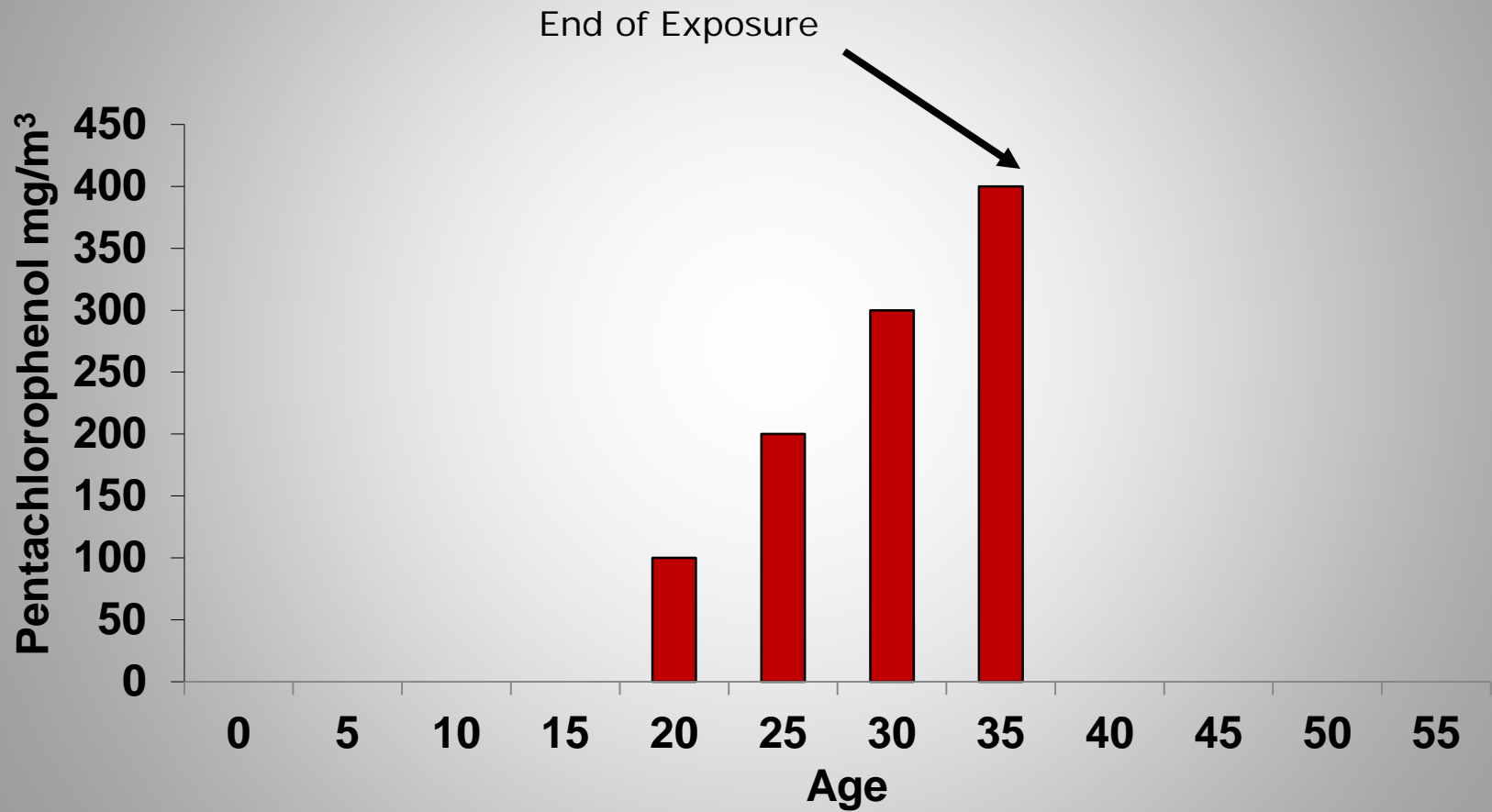
d. Time

- Work history

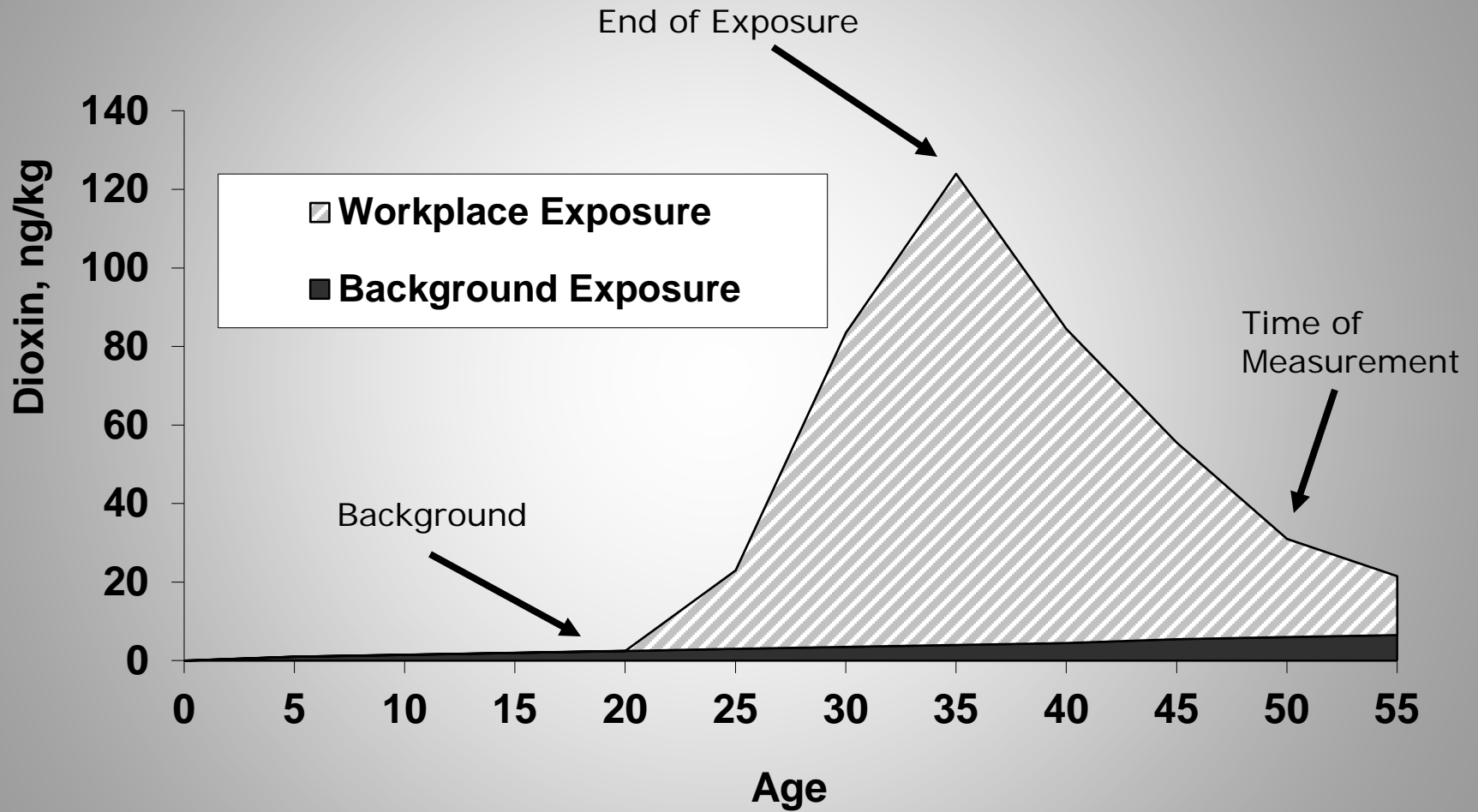
Exposure Modeling Issues

- If disease risk is thought to be proportional to dose then a cumulative exposure model may be appropriate
- Induction time analyses may be necessary to study cancer risk
- Internal versus external comparisons
 - Internal comparisons
 - usually reduce the healthy worker effect (selection bias)
 - allow direct comparison of relative risk across strata.
 - External comparisons
 - based on regional rates can adjust for geographic variability in social, cultural, and economic factors in relation to disease (Doll, 1985)
 - generally very stable.

Modeling of Pentachlorophenol Exposures



Modeling of Dioxin Exposures



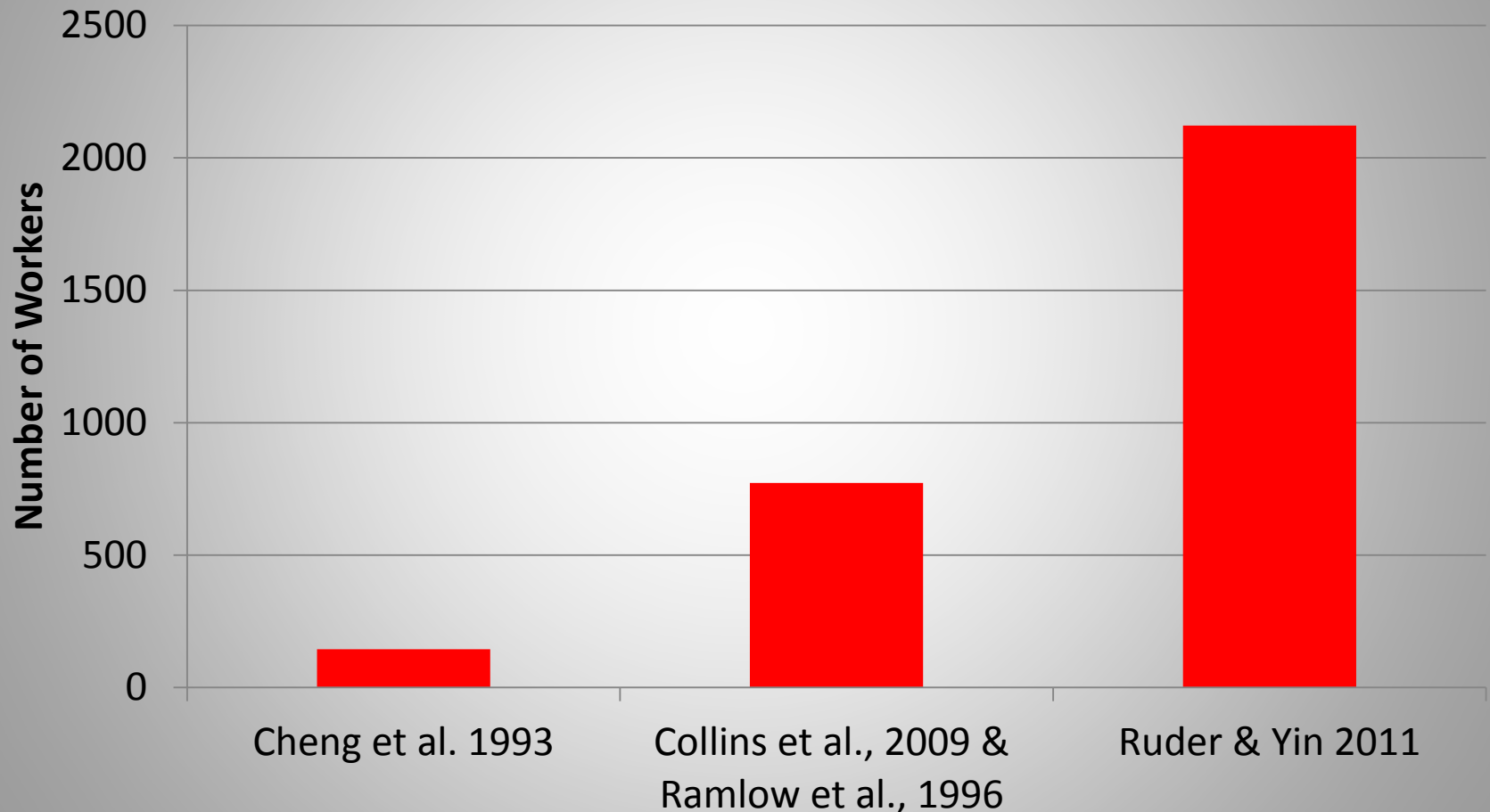
Exposure Estimation Approaches

1. Exposed/Unexposed
 - PCP w/contaminants (Cheng et al., 1993)
2. Duration of exposure
 - PCP w/contaminants (Hryhorczuk et al., 1998)(Ruder & Yin, 2011)
 - Dioxins (Kogevinas et al., 1997)*
3. Estimation using expert opinion and industrial hygiene monitoring
 - PCP & dioxins (Ramlow et al. 1996)
4. Modeling from biomonitoring
 - Dioxins (Flesch-Janys et al. 1998; Boers et al. 2010)*
(Collins et al. 2009)

Summary

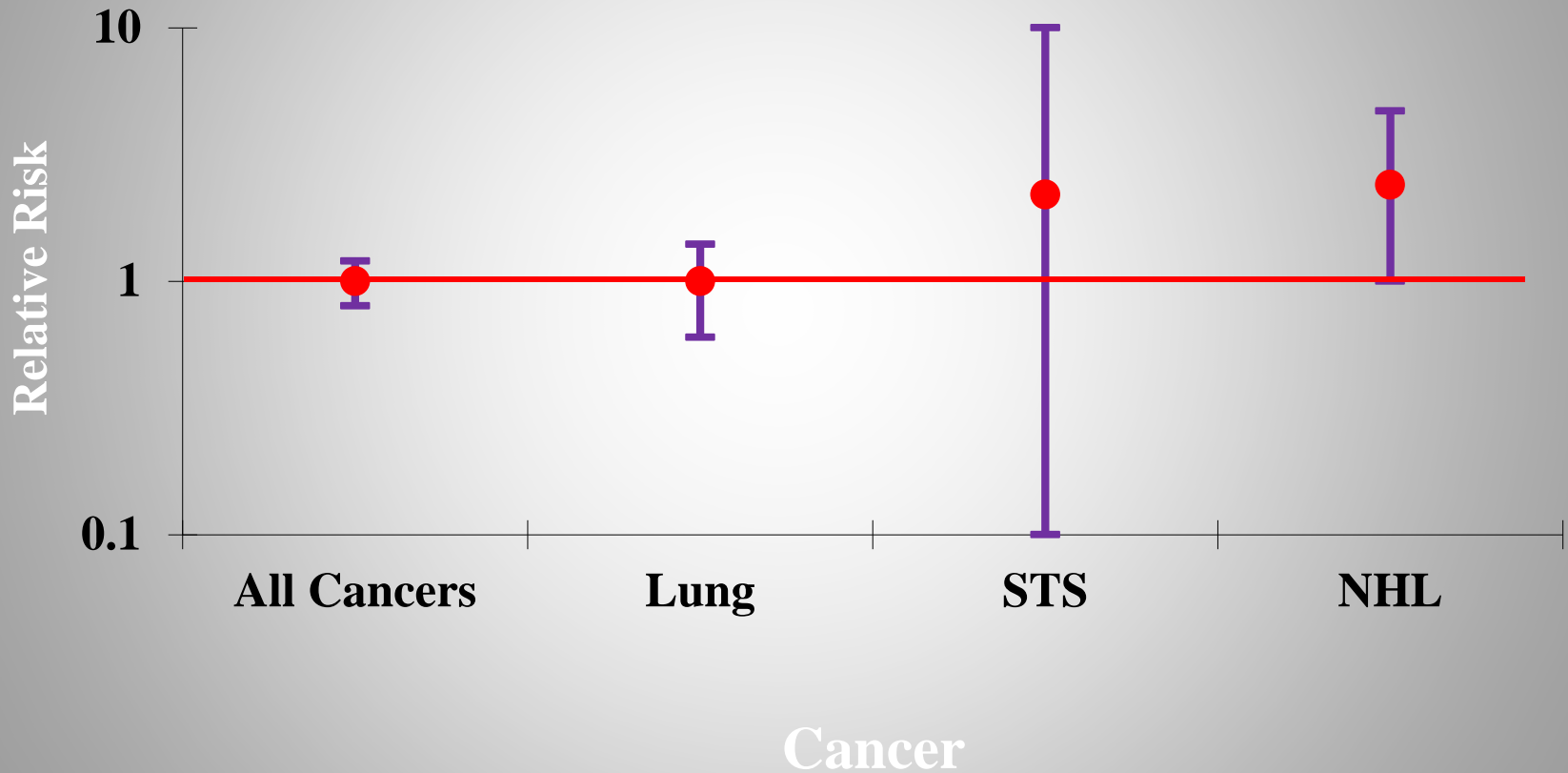
- Few studies have examined cancer risk in PCP production workers
 - Exposure characterization is mostly crude
- Few studies have examined serum dioxin levels in PCP exposed workers
 - While there has been several studies which examined TCDD, few studies even tried to measure the higher chlorinated dioxins

Only 3 PCP Industrial Workers Studies Examined Cancer Rates



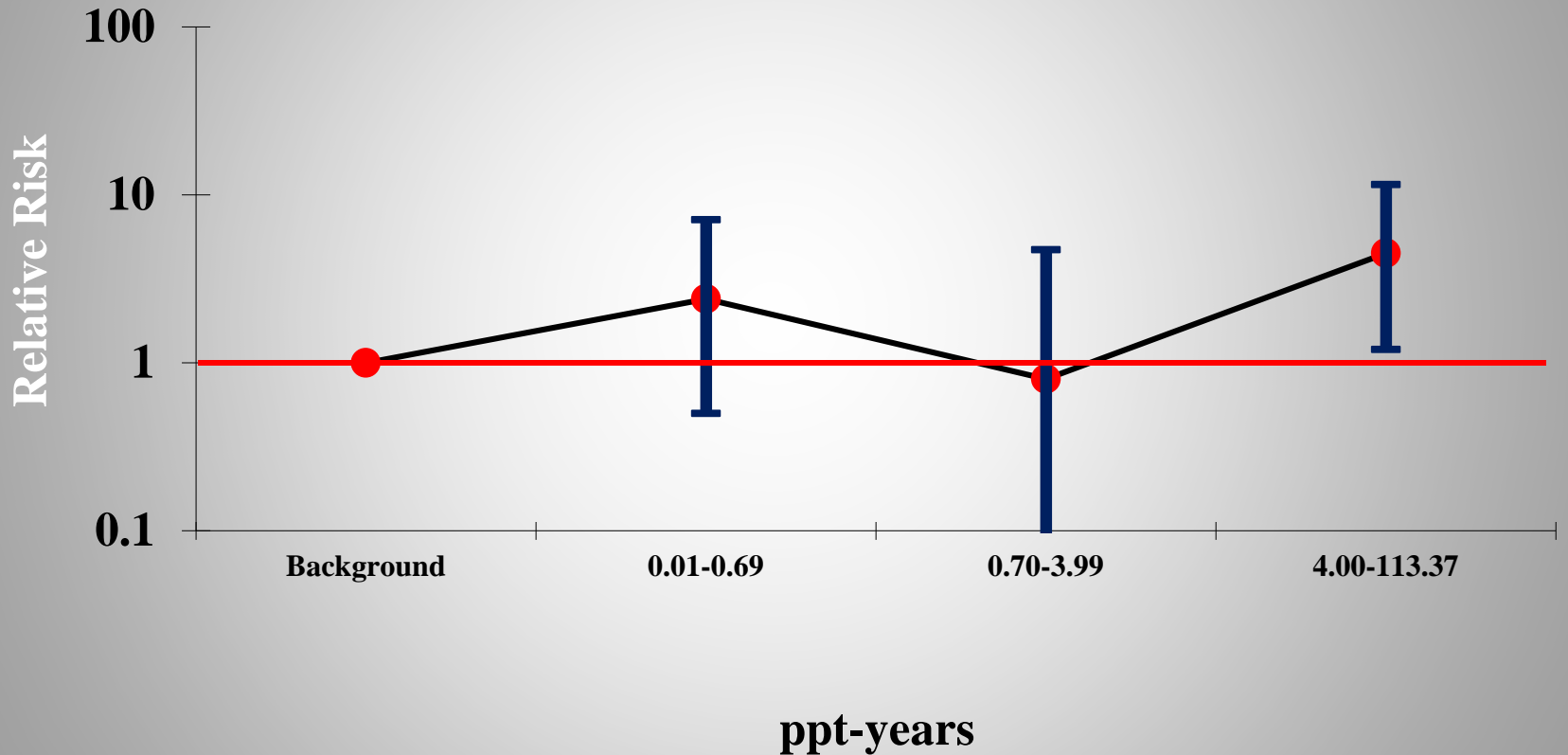
PCP STUDY RESULTS – MIDLAND, MICHIGAN (DOW)

Relative Risk & 95% Confidence Interval of Cancer Among Dow's **Pentachlorophenol** Workers using IARC Cancers of Concern



Source: Collins et al. 2009

Relative Risk & 95% Confidence Interval for Non-Hodgkin Lymphoma



Dow PCP Worker Studies

- Dioxin exposures among Dow PCP workers were well above background
 - Chloracne present in 20% of PCP workers
 - Extensive serum dioxin evaluations including serial serum samples
- Detailed work histories for all workers
- Long follow-up (1940-2003) and low loss during follow-up
- Our findings are consistent with other studies of highly exposed persons

Conclusions

- “Other than possibly an increased risk of non-Hodgkin lymphoma, we find no other causes of death related to the mixture of dioxin contaminants found in PCP.”
- All cancers combined and lung cancer at expected levels
- For NHL
 - No trend with exposure
 - NHL risk greatest in highest exposure category (only 4 deaths)
 - Other studies have not consistently found increase in NHL