

# **Risk Assessment of Environmental Chemicals: Integration of Epidemiology and Toxicology**

主辦單位：國家衛生研究院 國家環境毒物研究中心

協辦單位：國立台灣大學 生命科學院

時間：102 年 11 月 1 日

地點：國立台灣大學生命科學院大樓 3F 332 教室

# **Risk Assessment of Environmental Chemicals:**

## **Integration of Epidemiology and Toxicology**

時間：102 年 11 月 1 日

地點：國立台灣大學生命科學院大樓 3F 332 教室(台北市羅斯福路四段 1 號)

講者：Dr. Anna Fan (美國加州環保署)[英文授課]、郭育良教授(國立台灣大學環境職業醫學科及職業醫學工業衛生研究所)

目的及內容：近年來台灣發生多起環境毒物污染或人為蓄意添加造成食物污染之事件，引起民眾對其健康風險之疑慮，因此急需進行相關研究，以釐清環境毒物對國人健康影響之程度。為提昇台灣對此議題之研究能量，並學習其他國家處理類似議題之經驗，國家環境毒物研究中心邀請美國加州環保署的 Dr. Anna Fan 規劃系列課程。今年首次於 11 月 1 日開始一天的課程，授課者包括台大郭育良教授及 Dr. Anna Fan 兩位專家，將分別教授如何以流行病學及動物試驗的研究結果，評估暴露環境毒物之健康風險。

### Goals:

This will serve as the first of a series of lectures to address public health impacts of and protection from chemical hazards in our environment. The goals include, but are not limited to, the following:

- To discuss use of human, animal and other methodologies for evaluating chemical toxicity – current concepts and future perspectives
- To discuss how human and animal data and mode of action (MOA) considerations are used in health risk assessment and public health implications using case samples
- To discuss scientific basis of risk assessment as the foundation for risk management decision making – complexities, rigor and challenges
- To discuss integration of risk assessment (including risk characterization), risk communication and risk management in risk analysis
- To discuss issues on resources, expertise, timeliness, strategy and plan in meeting urgent vs. long-term needs for decision making

The aim is to achieve public health protection from chemical hazards through an understanding of these goals.

授課對象：政府、學校、民間機構內從事環境毒物或健康風險評估之工作或研究者，具基礎毒理學及流行病學知識。

報名方式：線上預約報名(座位有限，額滿為止)。全程參加者課程結束後給予上課證明。

課程內容：

9:30 – 9:40	致詞 Welcome-opening remarks	江宏哲 主任
9:40 – 10:20	Introduction 1. Methodologies for evaluating chemical toxicity – current concepts and future perspectives 2. Current issues – chemicals in food, water, air, workplace, waste site, other: Priorities and coordination	Dr. Anna Fan
10:20 – 11:35	The role of Epidemiology in Determination of Causality	郭育良 教授
11:40 – 13:00	Lunch	
13:00 – 13:50	Health risk assessment of As and CrVI and current issues	Dr. Anna Fan
13:50 – 14:40	Health risk assessment of perchlorate, melamine, and DEHP and current issues	Dr. Anna Fan
14:40 – 14:50	Coffee Break	
14:50 – 15:30	Significance of health risk assessments for management decision making - needs and strategies	Dr. Anna Fan
15:30 – 16:00	Planning for the future Concluding remarks	Dr. Anna Fan 林嬪嬪 副主任

主辦單位：國家衛生研究院 國家環境毒物研究中心

協辦單位：國立台灣大學 生命科學院

位置地圖及交通:

捷運-新店線公館站 2 號出口，往舟山路直行約 350 公尺

公車(捷運公館站)-207、208、672、673、907、綠 11、棕 12、敦化幹線(公車站牌地點為羅斯福路四段上捷運公館站 3 號出口前)



# Risk Assessment of Environmental Chemicals: Integration of Epidemiology and Toxicology

November 1, 2013

National Health Research Institute  
National Environmental Health Research Center

- Anna M Fan, PhD, DABT
- Chief
- Pesticide and Environmental Toxicology Branch
- Office of Environmental Health Hazard Assessment
- California Environmental Protection Agency
- Leon Guo, MD, MPH, PhD
- Professor
- Environmental and Occupational Medicine  
National Taiwan University (NTU)
- College of Medicine and NTU Hospital
- Professor
- Occupational Medicine and Industrial Hygiene,  
NTU College of Public Health

1

## Focus

1. 以流行病學及動物試驗的研究結果評估暴露環境毒物之健康風險 – case samples
2. How we connect risk assessment and risk management/regulatory decision making in a risk analysis framework (bridging the gap)

2

# Scope and coverage -1

- IS NOT step-by-step work-book type exercise given various formulae
- IS discussion of
- Evaluation of human data (strength of causal inferences from evidence)
- Experimental testing data/other methods (current and future)
- Risk assessment results of chemicals using human and animal data
- Single chemical cases – how each is unique and differs from each other
- Issues to anticipate – not straight-forward (e.g., data - adequacy, exposure, relevance etc.; interested parties – scientific community, government agencies, public, industry, media, legislature, legal etc.)
- Risk characterization
- Public health impact/protection
- Decisions/regulatory actions in face of evidence or uncertainty
- Education and outreach
- Risk communication
- Actions – coordination, timeliness, priorities and resources
- What do risk assessors need
- Who do risk managers need

3

# Scope and coverage - 2

- **Initially:**
- Discussion not meant to be comprehensive or to provide all perspectives on the topics
- Intends to highlight some important aspects
- **Future:**
- Opportunities for further discussion

4



# The role of Epidemiology in Determination of Causality

Y. Leon Guo

Environ & Occup Med

National Taiwan University (NTU) &  
NTU Hospital

Occup Med & Indust Hygiene

NTU College of Public Health

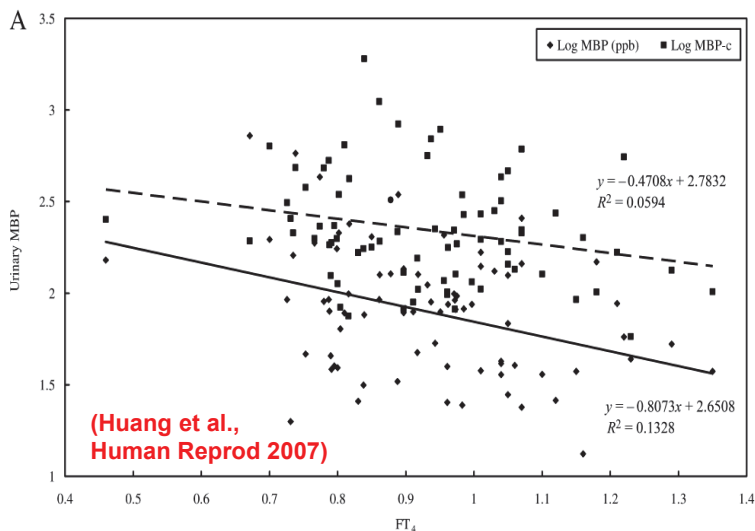


## Causal relationship demanded

- **Chan: reduced life expectancy growth in the neighboring counties of the 6<sup>th</sup> naphtha cracker industry**

# Causal relationship demanded

- In Taiwan, exposure to di(2-ethylhexyl) phthalate (DEHP) were found associated with precocious puberty, and reduced thyroid hormone in pregnant mothers



差很大! 塑化劑案求償78億 僅判賠120萬

TVBS-2013年10月17日 下午14:16

字級: 小 | 中 | 大 | 特 | 列印 | 轉寄 | 分享

發生在前年5月的塑化劑風暴還沒落幕, 消基會去年向新北地院提起團體訴訟, 幫539名消費者向統一等37家公司, 求償高達24億元, 這也是消基會有史以來求償金額最多的團體訴訟, 新北地院上午做出一審宣判, 判決37家業者, 總共賠償120多萬元, 有的公司只需賠償消費者9元, 因為精神損失部分通通不賠, 對於這樣的結果, 消基會律師表示遺憾, 會再上訴。

因為飲料含有塑化劑, 3年前悅氏董事長率領主管鞠躬道歉, 但法院判決出爐, 悅氏只須賠償消費者9元。悅氏董事長陳進原(2011.5.24): 「萬分的抱歉, 對不起。」

消基會去年替539名消費者, 向賣出塑化劑的37家廠商提出24億求償, 創下團體訴訟賠償金額, 但一審判決, 業者只要賠償120多萬, 法官認定, 業者只需要賠「產品」的價格, 所以悅氏賠9元, 台灣海洋深層水賠46元。新北地院庭長與李慶: 「承辦法官認為原告並沒有提出證據, 來證明損害的內容。」

除了舉證有難度外, 承審法官許瑞東認為, 根據衛福部的衛教資料指出, 塑化劑未過量, 24小時內就會排出, 對人體影響不大, 廠商只需賠償商品價格, 送驗費、健檢費、醫藥費、工作損失、懲罰性賠償以及精神損失通通免賠。塑化劑被害人莊小姐: 「應該說這些廠商完全一點良心都沒有, 很失望啊。」

司改會執行長林峯正: 「去參酌的一些官方宣導資料, 就認定一定會怎麼樣, 一定會怎麼樣, 我覺得有點草率吧。」

外界炮聲連連, 法官許瑞東, 司訓所30期畢業, 法官資歷已經20多年, 如今因為承辦塑化劑求償案, 備受矚目, 塑毒風暴還在延燒, 2年過去, 消費者的怒火還沒洩息, 如今判決結果更讓被害人質疑, 食品安全的問題, 到底要何時才能受到重視。



## 求償24億最後僅判賠120萬之法官見解

- 多數廠商 (被告) 於不知情下誤用含塑化劑之起雲劑, 無可罰性。
- 消費者 (原告) 並未充分舉證塑化劑暴露與健康損害間之因果關係, 故相關之醫療費、送驗費、工作損失與精神損失被告均免賠 - 舉證之所在, 敗訴之所在 -
- 衛生福利部國民健康署『食品中塑化劑污染衛教手冊』(李俊璋老師主筆): 人體試驗研究顯示DEHP進入人體後, 在12~24hr約有一半的量可快速代謝藉由尿液排出體外; 絕大部分的DEHP可於24~48hr由尿液或糞便排出; DINP亦會被人體迅速排出或代謝, 72hr內有85%由糞便中排出, 其餘部分主要由尿液排出。法官似由此認塑化劑並不會造成長期(慢性)之健康損害。
- 消費者購買含塑化劑商品屬實際損害, 判賠之120萬均為商品價金。

### 塑化劑事件鉅額求償判決小賠的關鍵

項目	法官不採納的理由
精神上損害賠償部分	衛生署國民健康局「食品中塑化劑汙染衛教手冊」, 明載塑化劑人體代謝後對健康並未造成損害
懲罰性賠償部分	1. 製造商是在不知起雲劑係遭昱伸、賓漢公司以塑化劑製造, 應無可罰的惡性 2. 要求其餘不知情的被告連帶負責, 並不適當 3. 消基會卻沒有舉證證明消費者受損害內容及金額

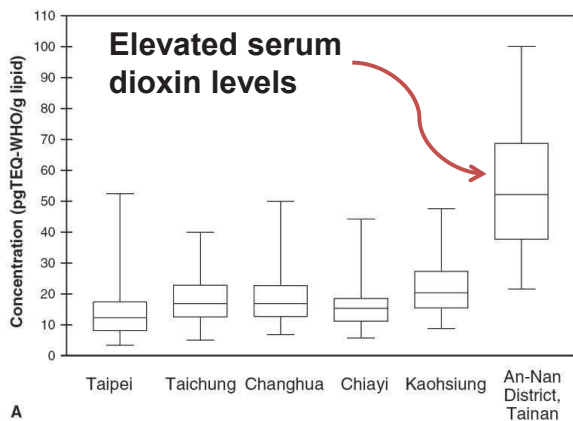
資料來源: 新北地院判決書

製表: 張國仁



# Causal relationship demanded

- In southern Taiwan, type 2 diabetes was alleged to be associated with exposure to dioxin-like chemicals through food exposure due to consumption of fish in a contaminated pond



A

www.iarc.fr/index.php

International Agency for Research on Cancer

ENGLISH FRANÇAIS

World Health Organization

05/03/2012 - Khaleej Times  
**Study shows danger of diesel exhaust**

04/03/2012 - Net India123  
**Diesel fumes may hasten lung cancer mort**

04/03/2012 - Yahoo! News  
**Study Links Exposure to Di**

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The International Agency for Research on Cancer (IARC) is part of the World Health Organization.

IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer prevention and control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.


**IARC News**

**IARC Postdoctoral Opportunities**  
02/03/2012 -  
Call for applications for a postdoctoral opportunity in the Section of Nutrition and Metabolism/Nutritional Epidemiology Group.  
**Deadline: 23/03/2012**  
Read more

**Industry group "threatens" journals to delay publications of important study on diesel engine exhaust**  
24/02/2012 -  
The Lancet Oncology reports today on an industry group "threatening" journals to delay publications that may be relevant for the forthcoming IARC Monographs meeting on Diesel and gasoline engine exhausts and some nitroarenes (Vol. 105, 5-12 June, 2012).  
Read more , The Lancet Oncology home page

Incidence, Cancer Mortality and Prevalence Worldwide

monographs.iarc.fr/ENG/Monographs/PDFs/index.php

**International Agency for Research on Cancer**  
  
**World Health Organization**

**IARC Monographs on the Evaluation of Carcinogenic Risks to Humans**  
<http://monographs.iarc.fr>

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Select link to view full volume and (since Volume 88) the *Lancet Oncology* summary

- Volume 100F (2012) Chemical Agents and Related Occupations
- Volume 100E (2012) Personal Habits and Indoor Combustions
- Volume 100D (2012) Radiation
- Volume 100C (2012) Arsenic, Metals, Fibres, and Dusts
- Volume 100B (2012) Biological Agents
- Volume 100A (2012) Pharmaceuticals
- Volume 99 (2010) Some Aromatic Amines, Organic Dyes, and Related Exposures
- Volume 98 (2010) Painting, Firefighting, and Shiftwork
- Volume 97 (2008) 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide)
- Volume 96 (2010) Alcohol Consumption and Ethyl Carbamate
- Volume 95 (2010) Household Use of Solid Fuels and High-temperature Frying
- Volume 94 (2010) Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins
- Volume 93 (2010) Carbon Black, Titanium Dioxide, and Talc
- Volume 92 (2010) Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures
- Volume 91 (2007) Combined Estrogen-Progestogen Contraceptives and Combined Estrogen-Progestogen Menopausal Therapy

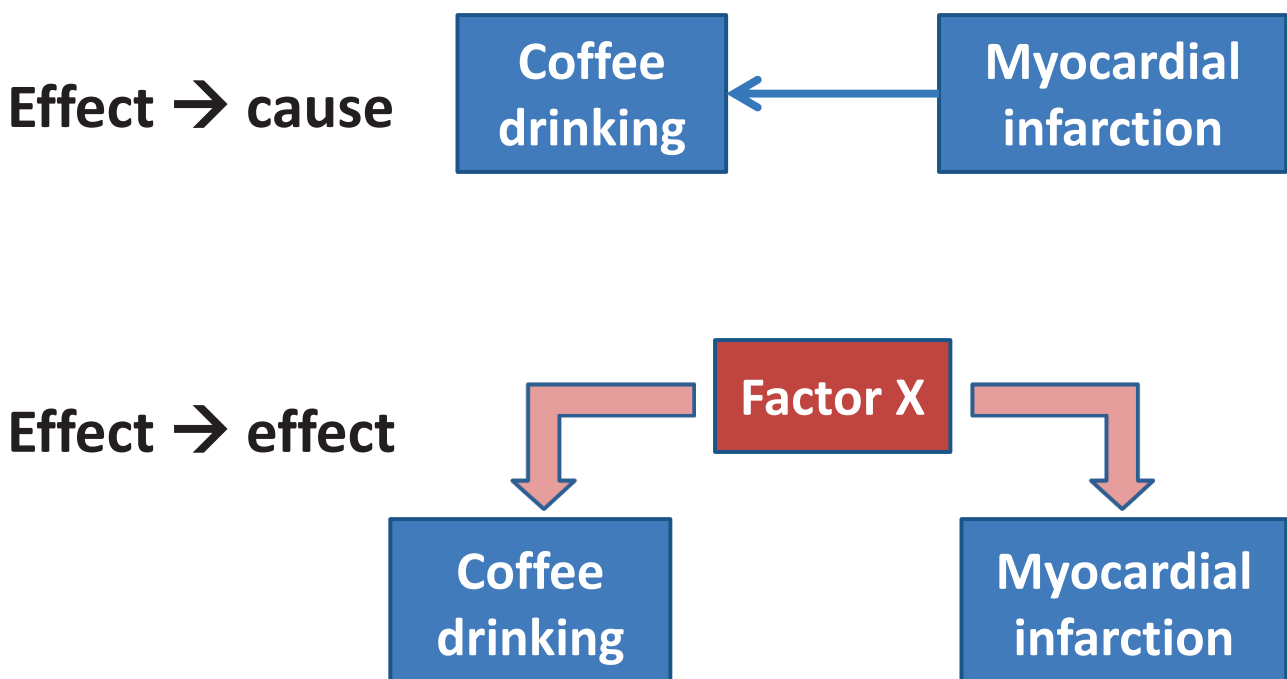
## Standard carcinogenicity classification by IARC International Agency for Research on Cancer

Group	Carcinogenic to humans	Human studies	Animal studies	Mechanisms in humans & animals
1	Definite	sufficient		
		<sufficient	strong	Relevant
2A	Probably	limited	sufficient	
		Inadequate	sufficient	Relevant
2B	Possibly	limited	<sufficient	
		inadequate	sufficient	
4	Not carcinogenic	negative	negative	
		inadequate	negative	
3	Un-classifiable	inadequate	Limited or inadequate	
		Inadequate	sufficient	Irrelevant
		Agents do not fall into any other group		

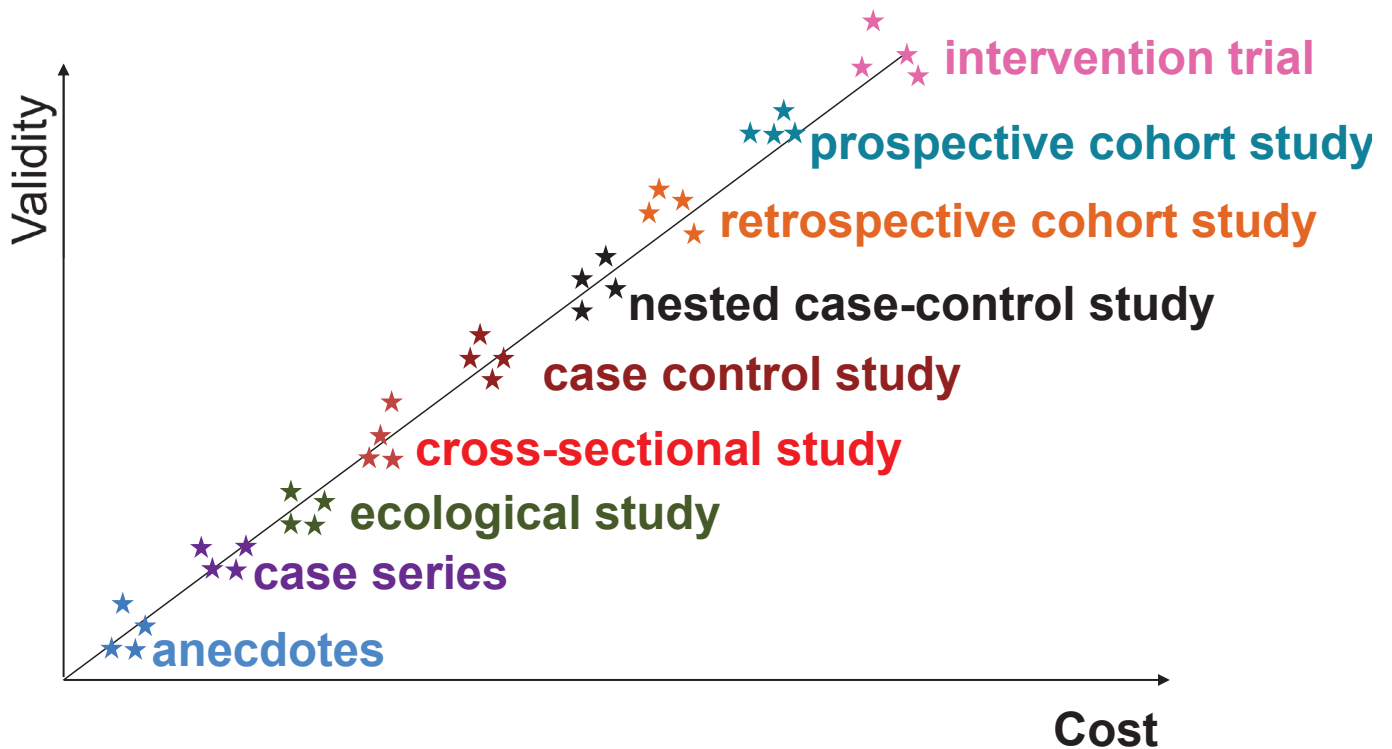
# Cause-effect relationship

- An aim of epidemiology: assessing cause of disease
- But most epidemiological studies are observational
- Possible explanations for an observed association:
  - Chance (random error)
  - Bias (systematic error)
  - Effect  $\rightarrow$  cause
  - Effect  $\rightarrow$  effect (confounding)
- Requires far beyond the data from a single study: magnitude of the association, the consistency of findings from other studies and biologic credibility.

## Observed association between coffee drinking and myocardial infarction

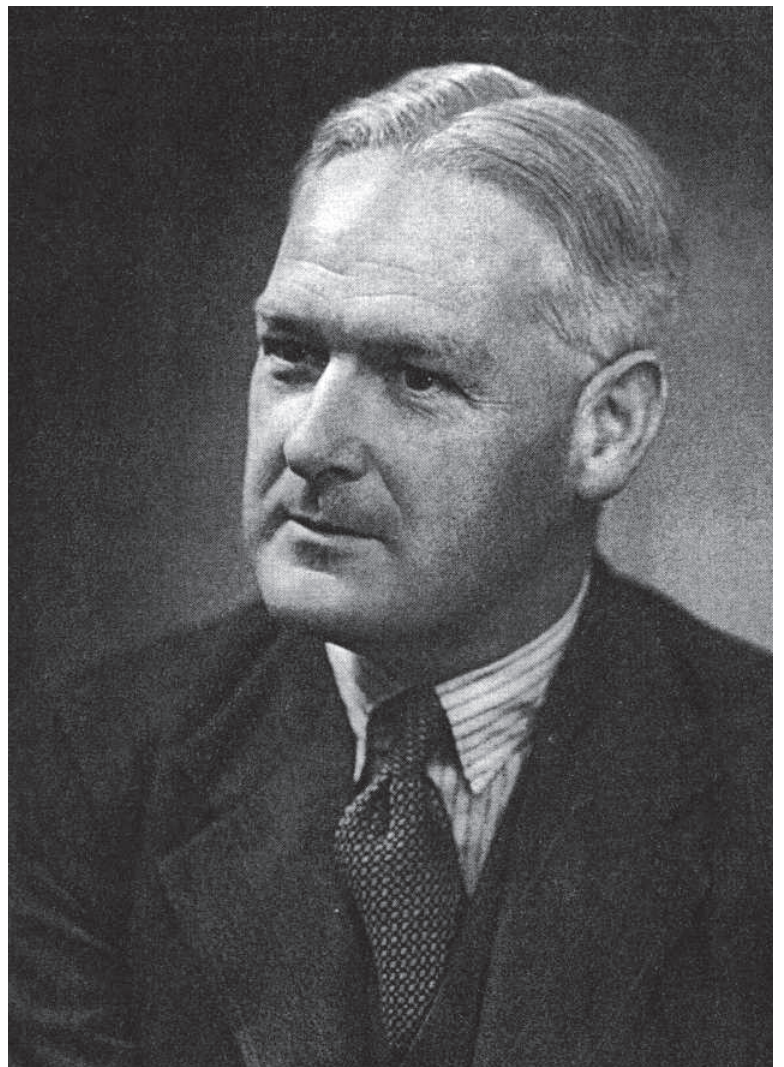


# Epidemiologic Study Designs



## Sir Austin Bradford Hill, 1897-1991

- English epidemiologist and statistician
- Professor, London School of Hygiene and Tropical Medicine
- Pioneered the randomized clinical trial
- Knighted in 1961
- Peter Armitage: "to anyone involved in medical statistics, epidemiology or public health, Bradford Hill was quite simply the world's leading medical statistician."



*Proceedings of the Royal Society of Medicine, 58 (1965), 295-300.*

### **The Environment and Disease: Association or Causation?**

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS  
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to

*Meeting January 14 1965*

### **President's Address**

observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What

## **The Bradford-Hill criteria** (**J Roy Soc Med 1965:58:295-300**)

### **1. Strength of the association.**

The stronger the association between a risk factor and outcome, the more likely the relationship is to be causal.

### **2. Consistency of findings.**

Have the same findings been observed among different populations, in different study designs and different times?

### **3. Specificity of the association.**

There must be a one to one relationship between cause and outcome.

#### **4. Temporal sequence of association.**

Exposure must precede outcome.

#### **5. Biological gradient.**

Change in disease rates should follow from corresponding changes in exposure (dose-response).

#### **6. Biological plausibility.**

Presence of a potential biological mechanism.

#### **7. Coherence.**

Does the relationship agree with the current knowledge of the natural history/biology of the disease?

#### **8. Experiment.**

Does the removal of the exposure alter the frequency of the outcome?

#### **9. Analogy**

# Scrutinized by Professor Kenneth Rothman, Boston University



- **Causation and Causal Inference in Epidemiology.**  
American Journal of Public Health 2005

- Professor in Boston University
- Renowned epidemiologist for >30 years
- American Public Health Association's Abraham Lilienfeld Award for 2002

## **Strength of the association** stronger association, more likely causal?

**BUT...**

- Hill himself acknowledged, that an association is weak does not rule out a causal connection
  - Cigarette smoking and cardiovascular diseases
  - Passive smoking and lung cancer, a weak association (20-30% increase) that few consider to be noncausal
- Counterexample
  - Down syndrome and birth rank
  - Confounded by the relation between Down syndrome and maternal age

# Consistency of findings

same findings among different populations?

**BUT...**

- The effect of a causal agent cannot occur unless the **complementary component causes** act, or have already acted, to complete a sufficient cause
- A common fallacy: some results are "statistically significant" and some are not

## Studies: relation between TCDD and diabetes

Chemical	Study description (n)	Outcome assessment	Adj OR (95% CI) <sup>a</sup>	Exposure contrast <sup>b</sup>	
Agent Orange	USA (AFHS ORH), diabetes in 2002; prospective, ♂ (776)	FBG, 2 hr-glucose	1.3 (1.1, 1.5) RR	2-fold increase in lipid adj (serum)	
Agent Orange	USA (AFHS ORH), diabetes up to 1992; retrospective, ♂ (989)	Phys dx	1.5 (1.2, 2.0) RR	High (initial > 94 ppt) vs. reference (current ≤ 10 ppt)	
Agent Orange	USA (Army), diabetes in 1999–2000; retrospective, ♂ (1,499)	Self-report	1.49 (1.10, 2.02)	Sprayer vs. nonsprayer	
TCDD	USA (AFHS ORH), diabetes up to 1995; CS, ♂ (169)	Self-report of Phys dx, OGTT	1.56 (0.91, 2.67)	Q4 vs. Q1 lipid adj (serum)	
TCDD	USA (AFHS ORH), diabetes up to 2004; retrospective, ♂ (1,020)	Phys dx, 2 hr glucose	1.39 (1.21, 1.58) HR	Pre-1969 vs. ≥ 90-day spray	

(Taylor et al., EHP 2013)



# Specificity

one cause → one outcome

- Unfortunately, the criterion is invalid as a general rule.
- Causes of a given effect cannot be expected to lack all other effects.

# Temporality

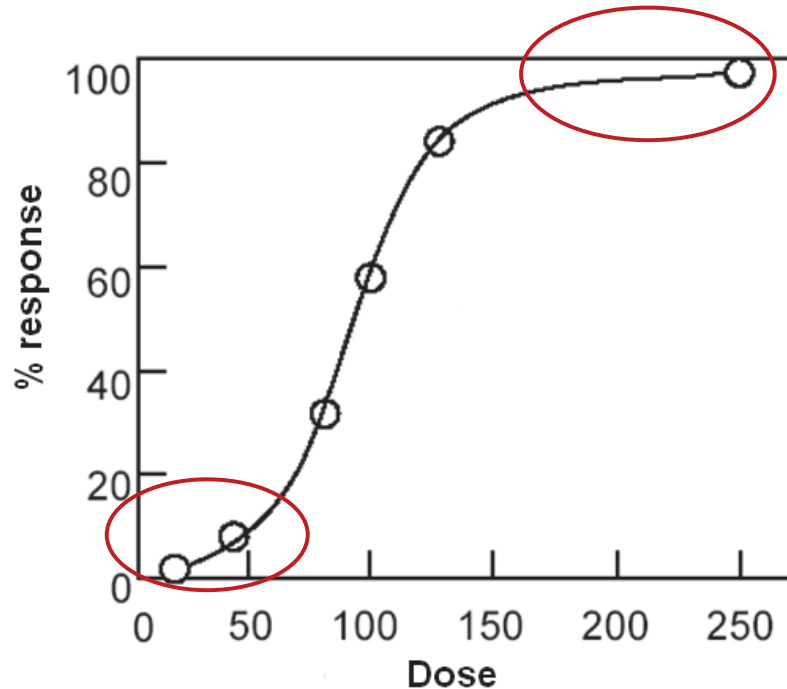
cause before outcome

- Inarguable!

# Biological gradient

## dose-response

- Presence of a unidirectional dose-response curve



## Yucheng (oil-disease) episode

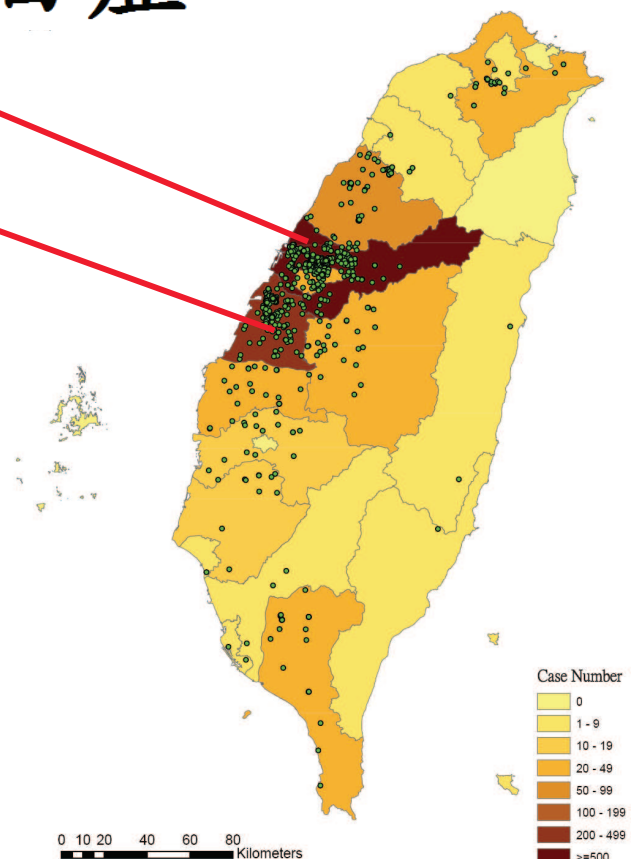
油症

TaiChung County

ChangHua County

- ◆ Outbreak in 1979
- ◆ Acne-form skin eruption, pigmentation of the skin and nail, hypersecretions of the Meibomian glands of the eyes
- ◆ Approximately 2000 victims involved

(Guo et al., *JTEH* 1994)



**Determination of whether women exposed to PCBs and PCDFs had higher risk of developing diabetes**  
**Reported diagnosed diseases as of 2003 (24 yr later, age 62)**

<b>% with diseases</b>	<b>Yucheng (n=332)</b>	<b>Reference (n=332)</b>	<b>AOR* (95% CI)</b>
<b>Type 2 DM</b>	<b>11.3</b>	<b>5.6</b>	<b>2.1 (1.1-4.5)</b>
<b>On therapy</b>	<b>7.7</b>	<b>3.2</b>	<b>2.5 (1.0-6.5)</b>

**\*Adjusted for age, BMI, smoking, and alcohol use**

**(Wang et al., Diabetes Care 2008)**

**Reported diseases ever diagnosed as of 2003, by chloracne, in Yucheng women**

<b>Chloracne</b>	<b>-- (n=186)</b>	<b>+ (n=58)</b>	<b>AOR* (95% CI)</b>
<b>Type 2 DM</b>	<b>5.9%</b>	<b>24.1%</b>	<b>5.5 (2.3-13.4)</b>
<b>Hypertension</b>	<b>14.4%</b>	<b>37.9%</b>	<b>3.5 (1.7-7.2)</b>
<b>Cardiovascular Diseases</b>	<b>11.8%</b>	<b>25.9%</b>	<b>3.0 (1.5-8.6)</b>
<b>Serum PCB (ppb)</b>	<b>73</b>	<b>121</b>	

**\*Adjusted for age, BMI, smoking, and alcohol use**

**(Wang et al., Diabetes Care 2008)**




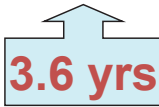


# Neurocognitive functioning

- Yucheng and control people aged 60 or above
- Neuropsychological test battery
  - Mini-mental state examination (MMSE)
  - Wechsler’s Adult Intelligence Scale (digit span and digital symbol)
  - Wechsler’s Memory Scale-Revised (WMS-R)
  - Geriatric Depression Scale, Short-form (GDS-S)
  - Bathel’s index of Activities of Daily Living (ADL)
  - Motor skill and tactile performance

## Neurocognitive testing in women

**VMR: -0.48/yr of age, adjusted for education**

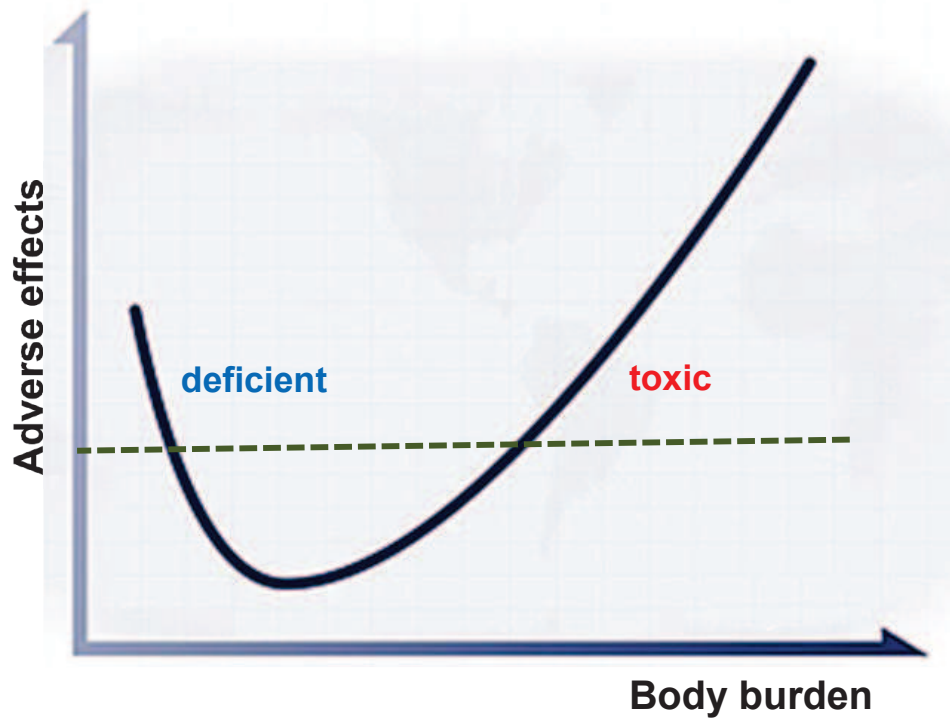
**VMS: -0.22/yr of age, adjusted for education**

Group Test	Controls (N=162)	≤ 30ppb (N=42)	30-90ppb (N=63)	≥ 90ppb (N=43)
<b>VMR</b> (p<0.05, test for trend)	29.1 ± 7.5	26.8 ± 7.3  4.8 yrs	26.5 ± 6.9  5.4 yrs	26.1 ± 8.6  6.3 yrs
<b>VMS</b> (p<0.05, test for trend)	10.8 ± 2.9	10.0 ± 2.5  3.6 yrs	9.7 ± 2.7  5.0 yrs	9.6 ± 3.2  5.5 yrs

\*Adjusted for age, sex, and education

(Lin et al., *EHP* 2008)

## J-shaped curve



## Biological plausibility

with reasonable biological mechanism

- an important concern but one that is far from objective or absolute

# Coherence

agreement with the current knowledge

- a cause-and-effect interpretation for an association **does not conflict with what is known of the natural history and biology of the disease**
- Hill emphasized that the absence of coherent information, as distinguished, apparently, from the presence of conflicting information, should not be taken as evidence against an association being considered causal.

# Experiment

removal of exposure changes outcome

- Seldom available
- As Popper emphasized, however, there are always many alternative explanations for the outcome of every experiment
- Example:
  - Hypothesis: malaria is caused by swamp gas
  - Experiment: draining swamps in some areas and not in others to see if the malaria rates among residents are affected by the draining.
  - Results: the rates drop in the areas where the swamps are drained.

# Analogy

- **Hill:** With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy.
- **Rothman:** handicapped by the inventive imagination of scientists who can find analogies everywhere. At best, analogy provides a source of more elaborate hypotheses about the associations under study; absence of such analogies only reflects lack of imagination or experience, not falsify of the hypothesis.

## What's useful

- **Strength of the association**
- **Consistency of findings**
- **Temporality**
- **Biological gradient**
- **Biological plausibility**
- **Coherence**

# Causality

- **Important principles such as**
  - **Multicausality**
  - **the dependence of the strength of component causes on the prevalence of complementary component causes**
  - **interaction between component causes**

## **Rothman's comments:**

- **Philosophers agree that causal propositions cannot be proved, and find flaws or practical limitations in all philosophies of causal inference. Hence, the role of logic, belief, and observation in evaluating causal propositions is not settled.**
- **Causal inference in epidemiology is better viewed as an exercise in measurement of an effect rather than as a criterion-guided process for deciding whether an effect is present or not.**



# “Causality” to be used where?

- Medical advices
- Policy making
- Occupational compensation
- Litigation evidence
- ...

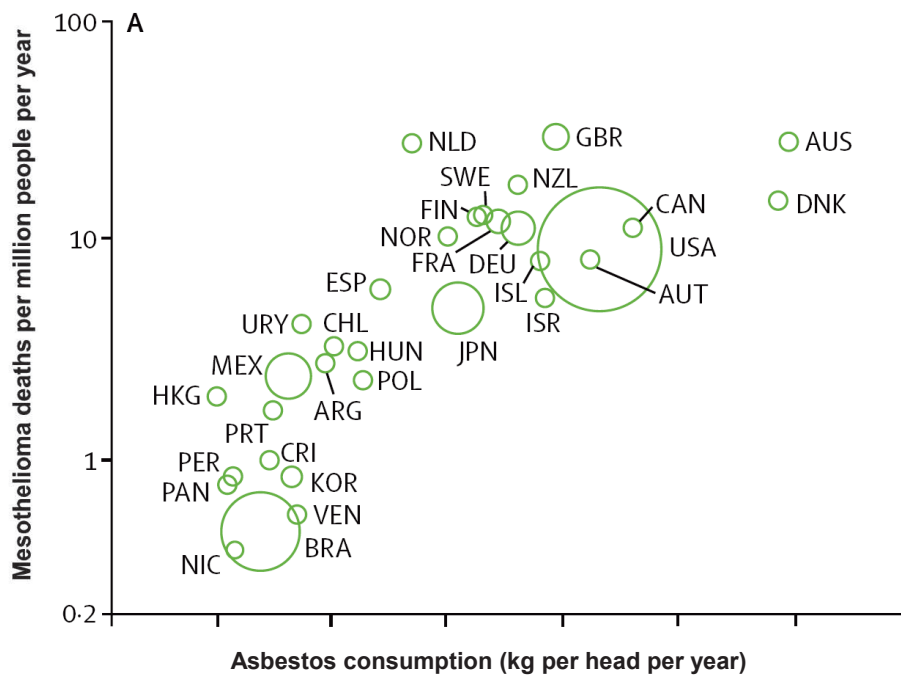
## “Causality” means?

### Three levels:

- Without the exposure, such disease would not have occurred
- If having this disease, 50% or more was induced by the exposure
- Increased risk by  $<100\%$

# Mesothelioma and asbestos

- Mesothelioma is a rare cancer caused almost exclusively by exposure to asbestos



(Lin et al., Lancet 2007)

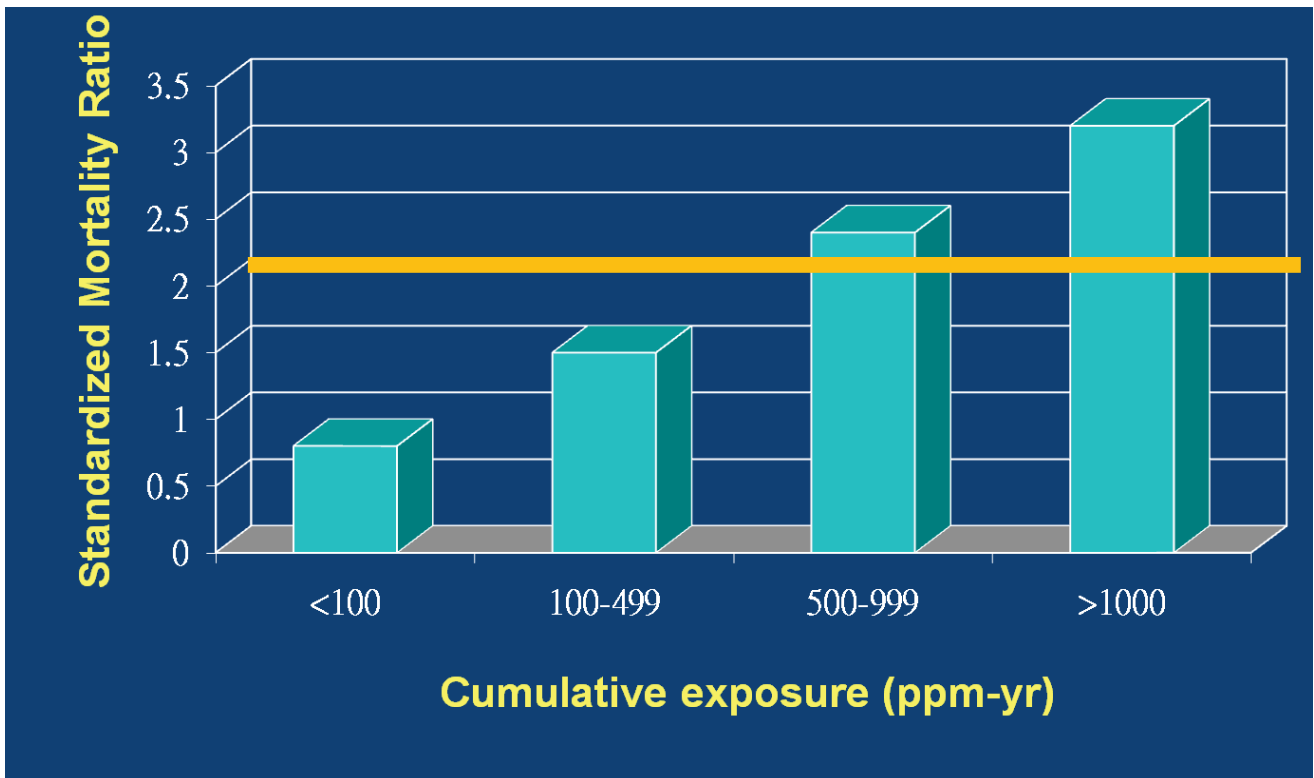
- 62 year old man with adenocarcinoma of the lung.
- He had worked in steel pickling industry for 20 years.
- Exposed to strong acid mist every day for 8 hours, 5-6 days a week.
- Never smoked
- Work-relatedness?

# More likely than not

- At the given exposure level the worker was exposed to, the **relative risk of having that cancer is at least 2 folds** of the unexposed workers
- From scientifically reliable literature

- **RR=1, then all cancers are caused by natural cause**
- **RR=1.5, then 1/3 of all cancers are caused by occupation, theoretically**
- **RR=2.0, then 1/2 (50%) of all cancers are occupationally related**
- **RR>2.0, then more than 50% of all cancers are occupationally related**

# SMRs for All Cancer Mortality by Exposure to Chemical A



## In other words...

- **Reliable evidence that the worker has been exposed to a total dose of chemicals responsible for causing a disease with relative risk of  $\geq 2$**
- **Adequate latency period**

## Cancer mortality in industrial cohort studies with high exposure levels (IARC, 1997)

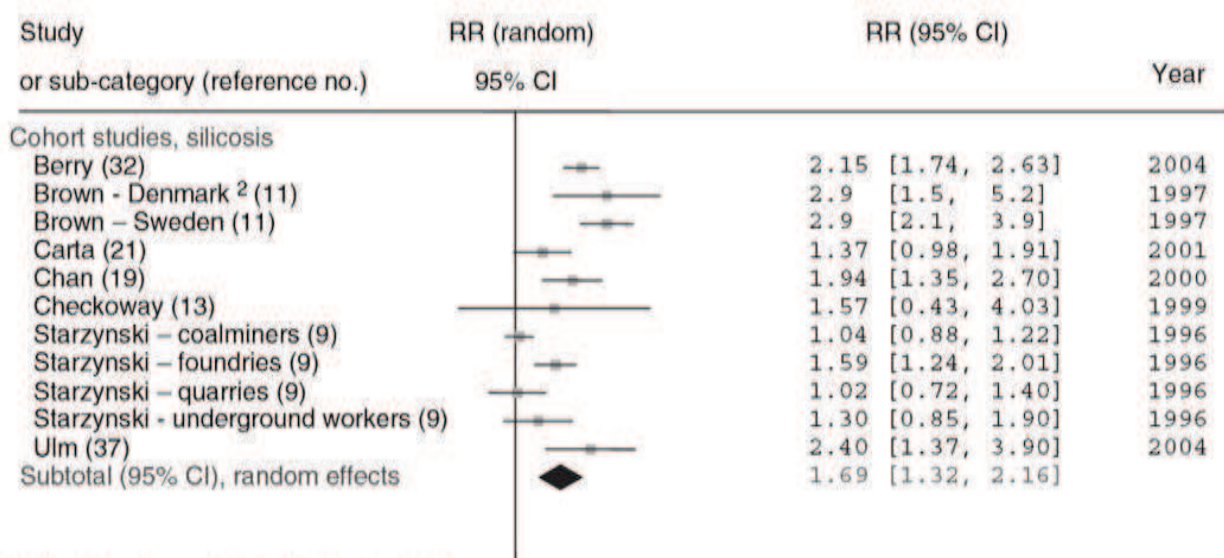
	ALL CANCERS			LUNG CANCER		
	Obs	SMR	95% CI	Obs	SMR	95% CI
FINGERHUT, 1991	114	1.5	1.2-1.8	40	1.4	1.0-1.9
BECHER, 1996	105	1.3	1.0-1.5	33	1.4	1.0-2.0
HOOIVELD, 1996	51	1.5	1.1-1.9	14	1.0	0.5-1.7
OTT & ZOBBER, 1996	18	1.9	1.1-3.0	7	2.4	1.0-5.0
<b>COMBINED</b>	<b>286</b>	<b>1.4</b>	<b>1.2-1.6</b>	<b>94</b>	<b>1.4</b>	<b>1.1-1.7</b>

$p < 0.001$

$p < 0.01$

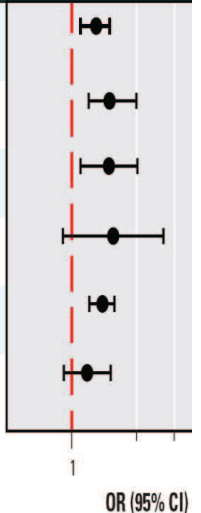
## Can exposure to silica cause cancer in the lung?

- Based on cohort studies, and among those with interstitial fibrosis (silicosis)



# Agent Orange or dioxin and diabetes in studies of Vietnam veterans

Reference	Chemical	Study description (n)	Outcome assessment	Adj OR (95% CI) <sup>a</sup>	Exposure contrast <sup>b</sup>
U.S. Air Force 2005	Agent Orange	USA (AFHS ORH), diabetes in 2002; prospective, ♂ (776)	FBG, 2 hr-glucose	1.3 (1.1, 1.5) RR	2-fold increase in lipid adj (serum)
Henriksen et al. 1997	Agent Orange	USA (AFHS ORH), diabetes up to 1992; retrospective, ♂ (989)	Phys dx	1.5 (1.2, 2.0) RR	High (initial > 94 ppt) vs. reference (current ≤ 10 ppt)
Kang et al. 2006	Agent Orange	USA (Army), diabetes in 1999–2000; retrospective, ♂ (1,499)	Self-report	1.49 (1.10, 2.02)	Sprayer vs. nonsprayer
Longnecker and Michalek 2000	TCDD	USA (AFHS ORH), diabetes up to 1995; CS, ♂ (169)	Self-report of Phys dx, OGTT	1.56 (0.91, 2.67)	Q4 vs. Q1 lipid adj (serum)
Michalek and Pavuk 2008	TCDD	USA (AFHS ORH), diabetes up to 2004; retrospective, ♂ (1,020)	Phys dx, 2 hr glucose	1.39 (1.21, 1.58) HR	Pre-1969 vs. ≥ 90-day spray
Steenland et al. 2001	Agent Orange	USA (AFHS ORH), diabetes up to 1995; retrospective, ♂ (990)	Phys dx, OGTT, FBG	1.18 (0.92, 1.52)	Exposed vs. nonexposed



(Taylor et al., EHP 2013)

## Different levels of epidemiologic evidence of causal relationship

- Levels sufficient to
  - trigger policy considerations
  - Provide medical advices
- Levels sufficient to
  - Provide evidence for occupational compensation
- Levels sufficient to
  - Provide evidence for litigation in court

**Even they are good studies with convincing results!**

# Risk Assessment of Environmental Chemicals: Integration of Epidemiology and Toxicology

Risk assessment, risk communication and risk management

November 1, 2013

National Health Research Institute  
National Environmental Health Research Center

- Anna M Fan, PhD, DABT
- Chief, Pesticide and Environmental Toxicology Branch
- Office of Environmental Health Hazard Assessment
  - California Environmental Protection Agency

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Methodologies for evaluating chemical toxicity  
– current concepts and future perspectives

- In vivo
- Human
- Animal
- In vitro
- Guidelines – testing
- Mode of action (MOA)
- Weight of evidence
- UF
- Benchmark dose
- Dosimetry
- Systematic review
- Exposure data
- Toxicity Testing in the 21<sup>st</sup> century
- Next Generation Risk Assessment:
- Incorporation of Recent Advances in Molecular, Computational, and Systems Biology
- MOA
- In silico
- ‘omics’ biomarkers
- High throughput
- AOP
- Exposure data
- Note: Not mutually exclusive, not comprehensive list

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# Risk assessment

Arsenic, Chromium VI, DEHP, Melamine, Perchlorate

- Scientific complexity (highly debated issues)
- Methodological differences
- Public health implications
- Regulatory significance
- National and international attention
- Addressing stakeholder concerns
- Coordination of scientific, public education and outreach, risk communication, regulatory and management activities

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		Non-Cancer		Cancer		Remarks
	Animal	Human	Animal	Human		
Arsenic	Skip	Skip	-	+		Human data (RA), worldwide Chem form/metabolism MOA
CrVI	Skip	Skip	+ oral	+ inh		IARC inh NTP oral Animal data (RA) CrVI vs CrIII MOA
DEHP	+	- limited	+	NA		Non-cancer Cancer assessment Animal data (RA) MOA
Melamine	+	+ Post incident	Skip	NA		Consumer/pets poisoning Animal data (RA) (MOA)
Perchlorate	Expt'l	+	NA	NA		Precursor effect Human data (RA) MOA

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# Arsenic

- Drinking water standard
- Maximum contaminant level, MCL = 10 ppb
- MCLG (goal) = 0
  
- Health Effects  
Skin, circulatory systems, increased risk of cancer
- thickening and discoloration of the skin, stomach pain, nausea, vomiting; diarrhea; numbness in hands and feet; partial paralysis; and blindness. Cancer of the bladder, lungs, skin, kidney, nasal passages, prostate
  
- Sources of contamination  
Erosion of natural deposits; runoff from orchards, glass & electronic production wastes, agricultural and industrial practices

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# Arsenic

## IARC

- 1980
- Classified "arsenic and arsenic compounds" in Group 1, which includes "chemicals and groups of chemicals, which are causally associated with cancer in humans"

## NRC

- 1999, 2001
- Taiwan data
- Bladder and lung cancer
- Excess risk estimates at 10 ppb arsenic
- Unit risks of  $1.2 \times 10^{-4}$  to  $2.3 \times 10^{-4}$  ( $\mu\text{g/L}$ )<sup>-1</sup> for lung cancer,  $1.4 \times 10^{-4}$  to  $1.8 \times 10^{-4}$  ( $\mu\text{g/L}$ )<sup>-1</sup> for bladder cancer

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# Arsenic

## USEPA

- 1998
- Two Taiwan studies
- Skin cancer
- Oral slope factor
- $1.5E+0$  per (mg/kg)/day
- Unit Risk  $5E-5$  per (ug/L)

## Cal/EPA

- 2004
- Studies in Taiwan, Argentina, Chile
- Bladder and lung cancer
- Oral cancer potency  $9.5$  (mg/kg-d)<sup>-1</sup>
- Unit risk  $2.7 \times 10^{-4}$  (μg/L)<sup>-1</sup>

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## Issues to address

- Generic
- Scientific
- Education and outreach
- Risk communication
- Regulatory
  
- Specific
- As in apples n apple juice
- As in rice
- As in chicken

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# Chromium VI

- IARC Carcinogen 1990
- Inhalation (lung and gastrointestinal cancers in workers)
- Oral?
  
- OEHHA – evaluate as a chemical in CA drinking water. Takes years.
- Animal, epidemiologic data (China Jinzhou - increased rates of stomach cancer, high levels in drinking water. Other.)
  
- NTP 2008 – Positive, rats and mice, gastrointestinal tumors
- National Toxicology Program study, OEHHA nomination for testing
- Public Health Goal (PHG) 2011. Oral cancer slope factor of 0.5 (mg/kg-day)<sup>-1</sup> based on a dose-related increase of tumors of the small intestine in male mice. First in the nation
  
- Scientific debate/discussion on-going

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# MOA

- Why some animal data do not apply to humans
  
- Mode of Action (MOA)
- Relevance to humans
  
- MOA – A focus of USEPA's Cancer guidelines 2005
- Defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation
- A key event is an empirical observable precursor step, that is itself a necessary element of the mode of action or is a biologically based marker for such an element.
  
- Whether human risk should be estimated using linear or non-linear extrapolation

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# DEHP

- Phthalic acid or benzene-1,2-dicarboxylic acid
- Dialkyl esters of phthalic acid or phthalate esters
- Di-2-ethylhexylDi-2-ethylhexyl phthalate (DEHP)
- Dimethyl phthalate (DMP)
- Diethyl phthalate (DEP)
- Di-n-butyl phthalate (DnBP or DBP)
- Di-iso-butyl phthalate (DiBP)
- Di-iso-nonyl phthalate (DiNP)
- Di-n-Octyl phthalate (DnOP or DOP)
- Butylbenzyl phthalate (BBP)
- Potassium hydrogen phthalate (KHP)

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# DEHP

- Phthalates
- Uses:
- PVC plasticizer, adhesives, solvent, fixative
- PVC products (DEHP), packaging materials, printing inks, personal care products/cosmetics (DEP, DBP), pharmaceuticals , electric cords/wires, auto leathers, floorings, construction materials, toys (DINP), footwear, sealants, paintings, coatings

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# DEHP

	Animal	Human	Remarks
Male reproductive effects	Adequate	Some	Testicular
Developmental effects	Adequate	Limited	
Female repro	Limited	Limited	
Endocrine/Thyroid function	Very limited	Limited	

# DEHP

- Toxicity and relevance
- Mice vs. rats vs. marmoset, different responses
- Are the rodent data relevant to humans?
- Metabolism
- Structure of the seminiferous epithelium
- Hormonal regulation of spermatogenesis
- Mode(s) of Actions (MOA) in rodent Postulations
- International assessments
- Intake levels – US, UK, Denmark, China
- Permissible levels – Australia, China, EFSA, OECD, UK, US, WHO

# Melamine

- USES
- White or colorless crystals used in manufacturing of dishes, plastic resins, flame-retardant fibers, components of paper and paperboard and industrial coatings
- Limited exposure in foods from food contact substance uses
- estimated level of melamine in food resulting from all of these uses is less than 15 µg/kg (0.015 ppm)
- Trichloromelamine is approved for use as a sanitizing agent on food processing equipment and utensils, except for milk containers and equipment
- Trichloromelamine readily decomposes to melamine during its use as a sanitizer. Only very low levels of melamine in food would be expected to result from this use
- No approved melamine use in direct addition to human or animal food in the U.S., nor is it permitted to be used as a fertilizer in the U.S., as it is in some parts of the world

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# Melamine

- Low toxicity in animal testing
- Acute kidney injury in human infants
- Mechanism of nephrotoxicity unknown
- Pathogenesis different in pets and humans

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# Melamine

- Melamine and cyanuric acid present in pet food
- Incomplete reactions during melamine production could lead to the formation of cyanuric acid, ammeline, and ammelide as co-contaminants in pet food
- When these melamine analogues, especially cyanuric acid, are available in the kidney, they can combine to form crystals in animal bodies and cause renal pathology

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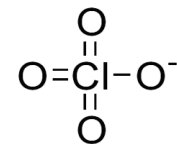
# Melamine

- Global attention
- Coordination among multiple agencies/nations in information sharing and risk assessment
- USFDA used a worst-case exposure scenario based on half of total daily dietary intake of liquid and solid food contaminated with melamine and its analogues. Multi-agency effort.
- Importance of
  - Chemistry and analysis of melamine and analogues in food for risk assessment
  - Immediate actions, public health decisions
  - Uniform nationwide standards
  - Regulations, laws and enforcement
  - Awareness
  - Ethics
  - Values

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# Perchlorate

- A principal oxidizer in solid rocket and missile fuels
- Used in explosives, fireworks, road flares, air bag inflation systems
- Highly soluble and mobile in water
- Physiological half-life = 8 hours
- Long shelf life
- Little biodegradation in the environment
- Found in drinking water sources and food samples



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# Perchlorate

- Inhibits iodine uptake into thyroid
- High doses - affect thyroid hormone levels and retard development
- Potential sensitive populations - pregnant women, fetuses and infants; women with low iodide consumption or hypothyroidism; infants receiving high doses
- Precursor effect

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# Perchlorate

- Inhibition of thyroid iodide uptake
  - The first event in the chain of anti-thyroid effects
  - Reversible inhibition of sodium iodide symporter (NIS)
  - An undesirable effect

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# Perchlorate

- Inhibition of iodide uptake could decrease thyroid function, may cause:
  - Decreased growth and cell metabolism
  - Goiter in pregnant women
  - Growth and mental retardation in infants
  - Thyroid tumors in rodents and aplastic anemia in humans (high doses)
  - At environmental concentrations, what adverse effects could perchlorate cause?

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# Perchlorate

- Regulatory action
- 2002- USEPA draft RfD of 0.00003 mg/kg-day, rat data
- 2005 - NAS committee reviewed USEPA risk assessment, recommended RfD of 0.0007 mg/kg-day, human data
- USEPA accepted NAS recommendation, but still must decide whether to regulate perchlorate
- MCL promulgation still ....

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## Education and outreach/risk communication

- **Interested parties**
  - Fact sheets
  - News release
  - Web posting
  - Workshops
  - Public informational mtgs
  - Legislative hearings, city council mtgs
  - Talked to concerned citizens via phone, community meetings
  - Talked with local officials
  - Received input from environmental groups, responsible parties, and legislators
  - Management discussion with other agencies, lobbyists, industry, media/reporters
  - risk managers/decision makers (legislature, legal)
  - Special meetings and planning with other govt programs (status update, sampling data, alerts, schedule, actions under consideration)
- **Scientific community**
  - Scientific peer review cycles
  - Presentations at special invitations, scientific meetings
  - Exchanged ideas with other scientific bodies

### **Who does what**

Different roles for different responsible agencies/depts/programs  
Different roles for external affairs/public information officer, managers, legal, scientific staff  
Principles and practice of risk communication  
Trust and credibility (and more)

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# From risk assessment to risk management

- **What do you do with the numbers?**
- Appropriate use with understanding of the basis (do not just cite and use the numbers)
- To determine seriousness of health concern
- To determine risk levels from risk assessment for possible risk management decisions (toxicology, exposure)
  
- **Interpreting risk levels**
- Who you are/your responsibility
- What you know
- Risk Perception
  
- **Risk management**
- **Responsible parties**
- What you know (from risk assessment)
- What decision do you need to make
- What the system can afford
- What is acceptable
- Who are the stakeholders
- Scientific, economic, technical, social, political factors
  
- **Education and outreach**
- **Risk Communication**
- Principles and practice
- Who to give
- Who to receive
- Situations

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## Significance of health risk assessments for management and regulatory decision making – needs and strategies

- **Significance of risk assessments**
  
- When do you need to do a risk assessment
- Why do you need to do risk assessments when other agencies are doing it
- What are other related activities (exposure, survey)
- RA capability – expertise, time and resource intensive
- What are the options - when urgent, or have limited staff/resources
- Still need experienced scientists to determine appropriateness for use of information specific to situation at hand

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# Future guidelines/protocol

- Is there a need for some form of guideline or protocol for responding to chemical situations (contamination or environmental release)?
  - Standard guidelines/protocols do not exist for all situations that can vary extensively
  - Any one set may not fit all
  - Often developed for specific needs
  - Emergency vs. non-emergency response
  - Can be developed especially after some experience gained and when future similar situations are anticipated
  - Partial adoption of existing similar guidelines/protocol with modifications
  - Depends on various factors
  - Examples?
- A consideration for the future

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## Why we need to train new talents and keep up with current state of knowledge

- Risk assessment is not straightforward
  - Many decision points
  - New toxicological findings
  - New methodologies
  - Advancement in understanding various aspects (e.g., mode of action)
  - Examples given to illustrate above
  - Same information (principles, concept, approach, methodology, considerations, etc.) can be applied to assessment of chemicals in food and other media, with situation-specific modifications (e.g., exposure)
  - Quality and credibility, ability to evaluate and interpret
  - Achieve international professional standard
  - Ability to meet future challenges relating to chemicals in our food supply and general environment
  - Support risk managers to make informed risk management decisions
- END

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