Contribution of epidemiology to occupational exposure limits

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Setting the stage

- Monson (1990): “role of the occupational epidemiologist must evolve into that of a person who assists in the setting of standards of exposure rather than that of a person who measures adverse effects of exposure”
- Burke (1995): “... epidemiology is currently playing an increasing role in contemporary regulatory issues. ... results of epidemiologic studies are being used by regulators to guide decisions. Shouldn't epidemiologists participate in determining how their data are applied?”

Background

- Exposure-response studies are hardly ever done out of mere scientific curiosity only
- Usually there is strong evidence that a substance causes one or more diseases
- It is important to quantify the risk of developing these diseases in response to different levels of average or cumulative exposure, or some other valid measure of exposure

Background

- The occupational epidemiologist knows and, in fact, expects that eventually a risk assessor will try to apply the study results in some practical, useful sense
- Epidemiologists should be effective risk communicators in the sense that they effectively transmit their results and recommendations to risk assessors and risk managers, especially if their work reliably suggests that a current OEL is inadequate to the task of protecting exposed workers

Meaning of OEL

- The OEL should correspond to the **upper limit** for each single shift time-weighted average exposure
- In this way the true long-term, working lifetime mean exposure of each employee is maintained at protective levels
- This also provides a practical means of accounting for the uncertainty in the risk assessment that led to the OEL

Meaning of OEL

- Once an OEL is established, exposure (risk) management should be viewed as a *quality* control problem
- The distribution of exposures for each worker should be controlled so that exposures never (or rarely) exceed the OEL
- Similar in concept to the medical management of non-occupational risk factors, such as elevated cholesterol
- Those charged with risk management responsibility should focus on ensuring that each employee is monitored at **regular intervals**

Components of OEL

- An OEL consists of three components:
  - concentration
  - averaging time
  - target (usually the individual worker)
- Example
  - In 1987 the Occupational Safety and Health Administration (OSHA) adopted a Permissible Exposure Limit (PEL) for benzene of 1 ppm, specifying the averaging time as a single shift, or 8 h/d, and the target as the individual worker
- All authoritative OELs in the US (OSHA's PELs, NIOSH's RELs, and ACGIH's TLVs) targeted to each individual worker

Changing the level of protection

- The level of protection will change if any of the components of an OEL - the concentration or the averaging time or the target - are modified from those originally defined
- The level of protection is increased when a company sets and meets an internal target concentration lower than the legal limit
- The level of protection is reduced if a company has a policy of using the average of multiple TWA measurements rather than a single shift

Risk assessment

- Qualitative or quantitative characterization of the potential health effects of particular substances on individuals or populations (NRC)
- Components
  - Hazard Identification
  - Dose-Response Assessment
  - Exposure Assessment
  - Risk Characterization
- Occupational epidemiology plays a role in each of these steps

Risk management

- Risk management involves ‘value judgments’ after considering the estimates of actual risk, the perceptions of risk present in exposed population and the target industries, and the benefits and costs of control measures
- Components of risk management
  - setting an OEL (concentration, averaging time, and target)
  - requiring a minimal level of baseline monitoring and occasional resampling
  - requiring that exposures be adequately controlled
  - requiring a minimal level of medical monitoring
  - occasionally auditing each company’s ability to manage risk for its workers

Extrapolating from cohort to individual - 1

- In occupational epidemiology, exposure assessment entails constructing job-exposure matrices or similar tools in order to determine the cumulative or average exposure of comparable groups of members of the cohort
- The exposure of an exposure group is assigned to each worker in that exposure group for each observation period
- Because individual workers move from group to group for differing amounts of time, the range of cumulative or average exposures can vary substantially, resulting in unique measurements and cumulative or average exposures
- The exposure-response analysis focuses on estimating the expected average risk corresponding to specific levels of **cumulative or average exposure**

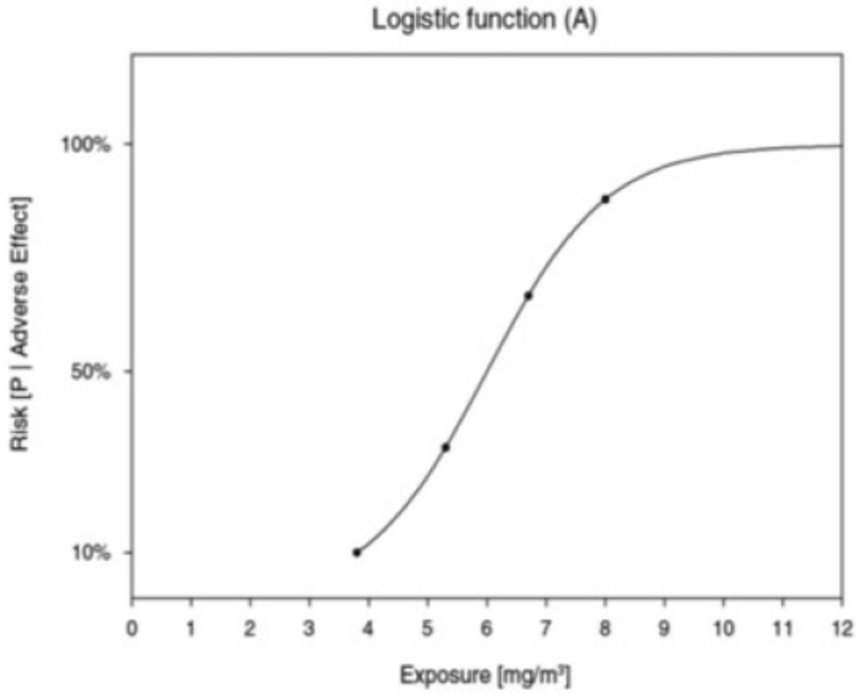
Extrapolating from cohort to individual - 2

- The level of risk at any average or cumulative exposure is an average level for the hypothetical group of workers included in that category
- Some individuals within this hypothetical group will experience a higher risk and others a lower risk
- The range of these differences will reflect the lack of knowledge regarding such factors as individual sensitivity, other exposures, and the fact that the estimates of exposure do not capture true individual exposure differences
- How can one translate an acceptable average or cumulative exposure for a hypothetical exposed group to an **individual worker**?

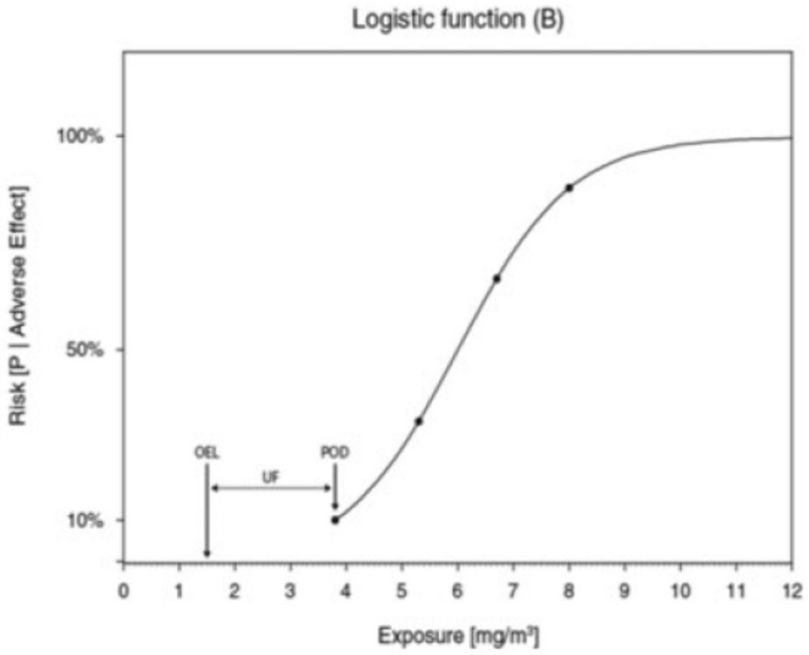
Extrapolating from cohort to individual - 3

- It is necessary to set an OEL that is considered protective for each exposed individual and not just some larger exposed population
- In practice, the upper limit of the 95% confidence interval is used, instead of the point estimate, to derive an OEL which is expected to protect most, if not all, exposed workers
- *The interpretation of this approach is not that 95% of the workers will be protected at the set value*

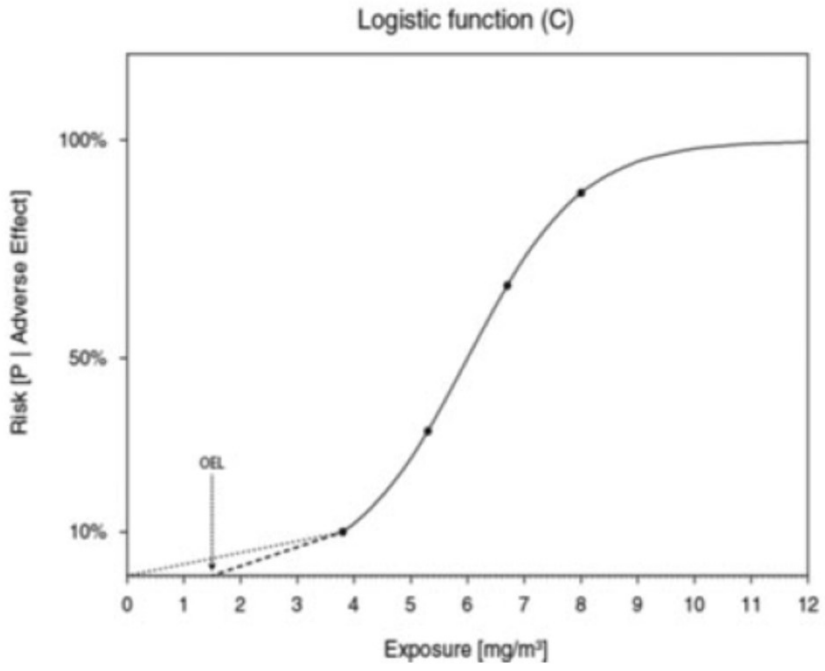
Low-dose extrapolation
Typical dose-response curve from epidemiology



Low-dose extrapolation - 1
Application of uncertainty factor (UF) from point of departure (POD) to estimate OEL

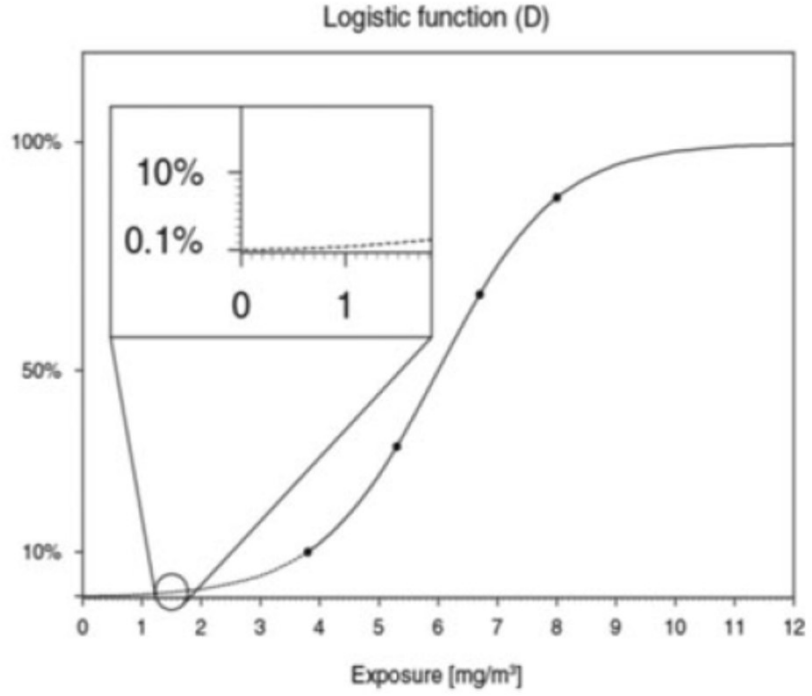


Low-dose extrapolation - 2
Linear extrapolation from the POD to an OEL or a hypothetical point of no excess risk

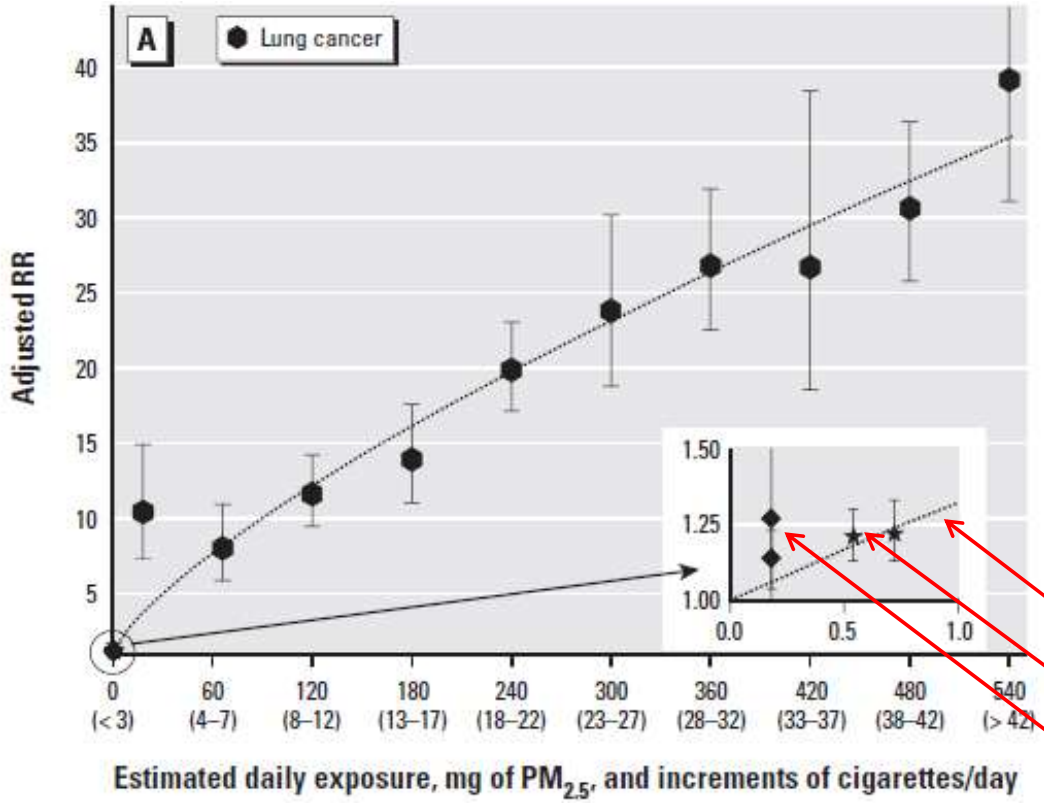


Low-dose extrapolation - 3

Alternative to linear extrapolation when the available data support the derivation of an exposure-response curve directly in the exposure region of interest



Example – PM2.5 and lung cancer



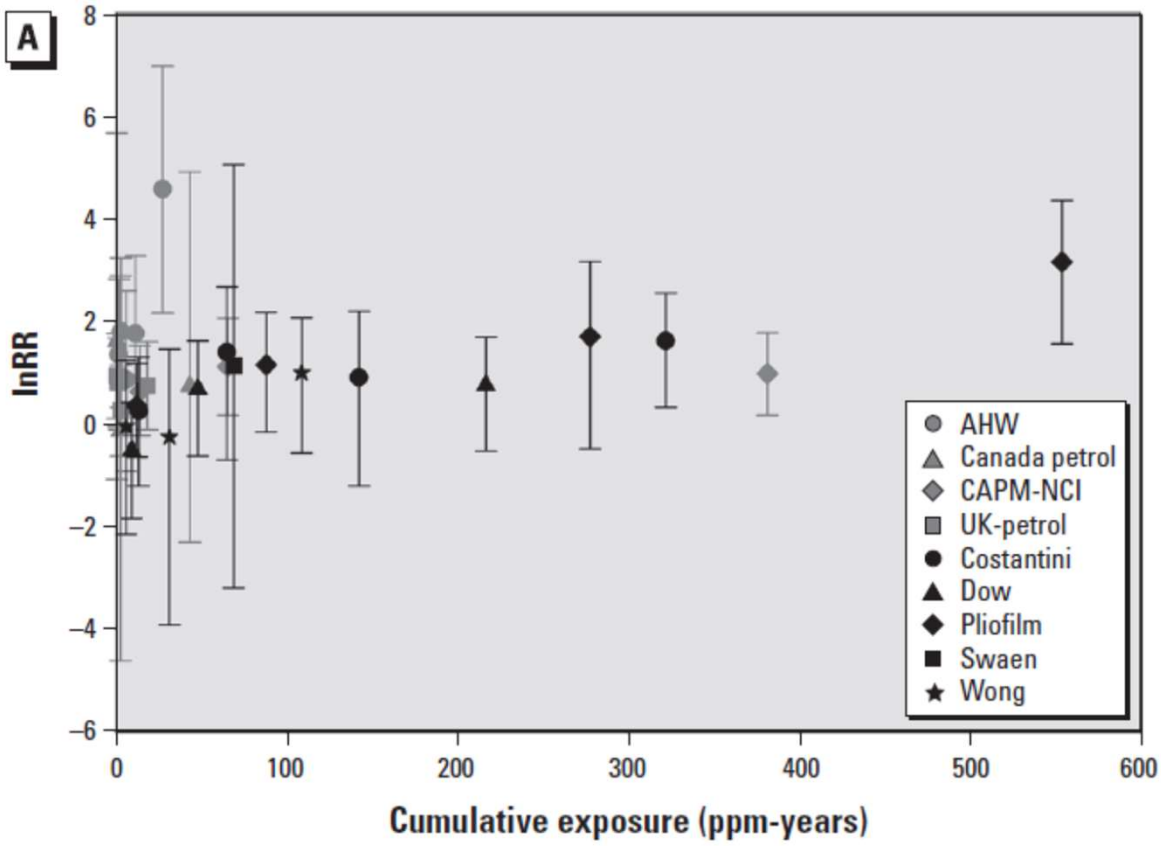
Extrapolation from smoking

Studies of second-hand smoke

Studies of air pollution

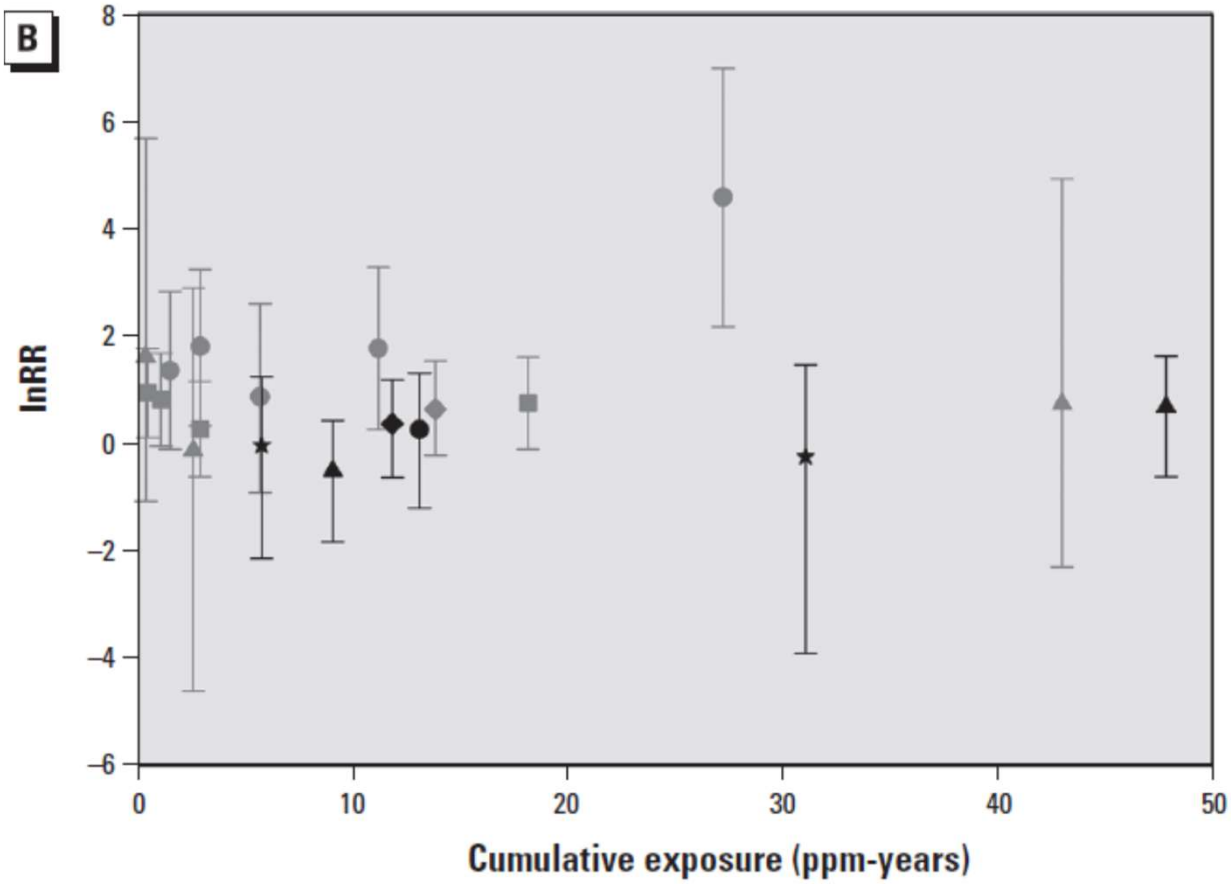
Pope et al., 2011, based on CPS-II data

Meta-regression on cumulative benzene exposure and risk of leukemia – Full exposure range

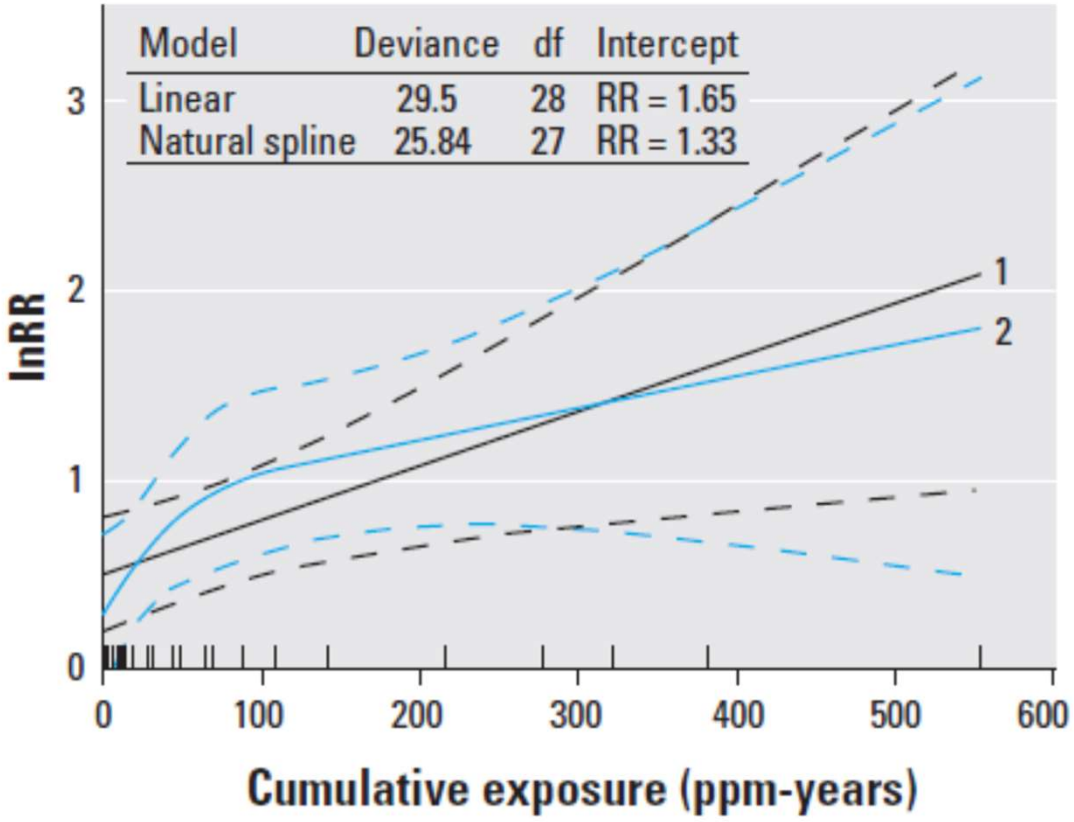


Vlaanderen et al., 2010

Meta-regression on cumulative benzene exposure and risk of leukemia – Exposure < 50ppm-yrs



Meta-regression on cumulative benzene exposure and risk of leukemia – Dose-response with intercept



Meta-regression on cumulative benzene exposure and risk of leukemia – RR at 10 ppm-yrs

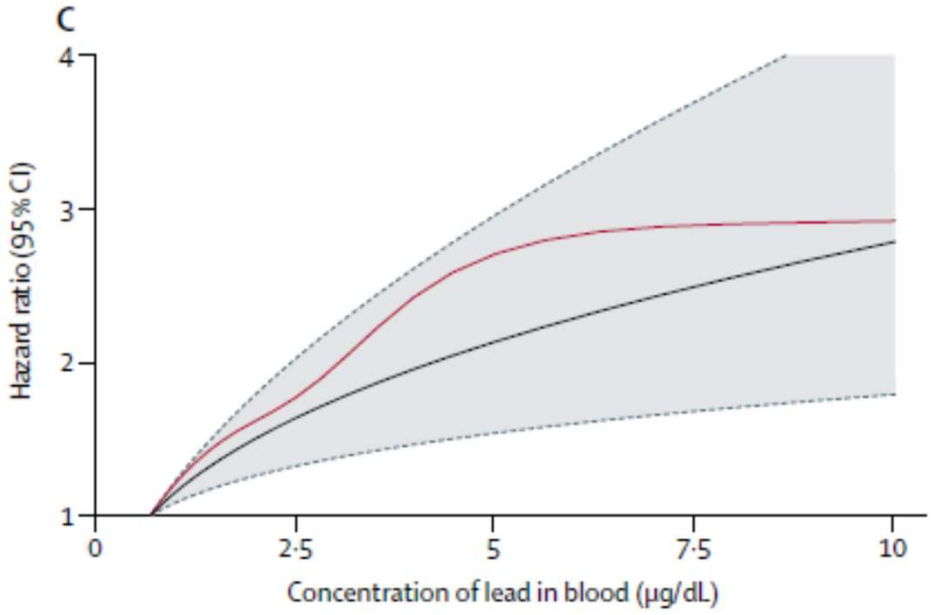
Model	Deviance (df)	Intercept	10 ppm-years
Prediction meta-regression—all studies			
Scenario A: natural spline	25.84 (27)	1.33 (0.87–2.05)	1.52 (1.08–2.15)
Scenario A corrected for intercept			1.14 (1.04–1.26)
Scenario B: natural spline without intercept	28.39 (28)	NA	1.22 (1.11–1.34)
Scenario D1: linear model without intercept	38.67 (29)	NA	1.05 (1.02–1.07)
Prediction meta-regression—cohort studies			
Scenario C: natural spline	8.43 (15)	1.13 (0.71–1.81)	1.25 (0.83–1.88)
Scenario C corrected for intercept			1.10 (1.04–1.17)
Scenario D2: linear model without intercept	15.95 (17)	NA	1.04 (1.02–1.07)

History of lead OEL

Agency	Air-Exposure Guideline (8-h time-weighted average)	Recommended Limit for Blood Lead Level	Year Approved
Occupational Safety and Health Administration	50 μg/m^3	40 μg/dL	1978
National Institute for Occupational Safety and Health	50 μg/m^3	60 μg/dL	1978
American Conference of Governmental Industrial Hygienists	50 μg/m^3	30 μg/dL	1987 (air) 1995 (blood)
European Council Directive 98/24	150 μg/m^3	70 μg/dL	1998
European Union Scientific Committee on Occupational Exposure Limits	100 μg/m^3	30 μg/dL	2002
German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area	None, because probably carcinogenic in humans	40 μg/dL for men and women over 45 years old 10 μg/dL for women under 45 years old	2006
United Kingdom Health and Safety Executive	150 μg/m^3	25 μg/dL for women of reproductive age 40 μg/dL for people 16-17 years old 50 μg/dL for all other employees	2002

Proposal of ACOEM to lower OSHA standard to 15 µg/dL (3.5 µg/dL in women)

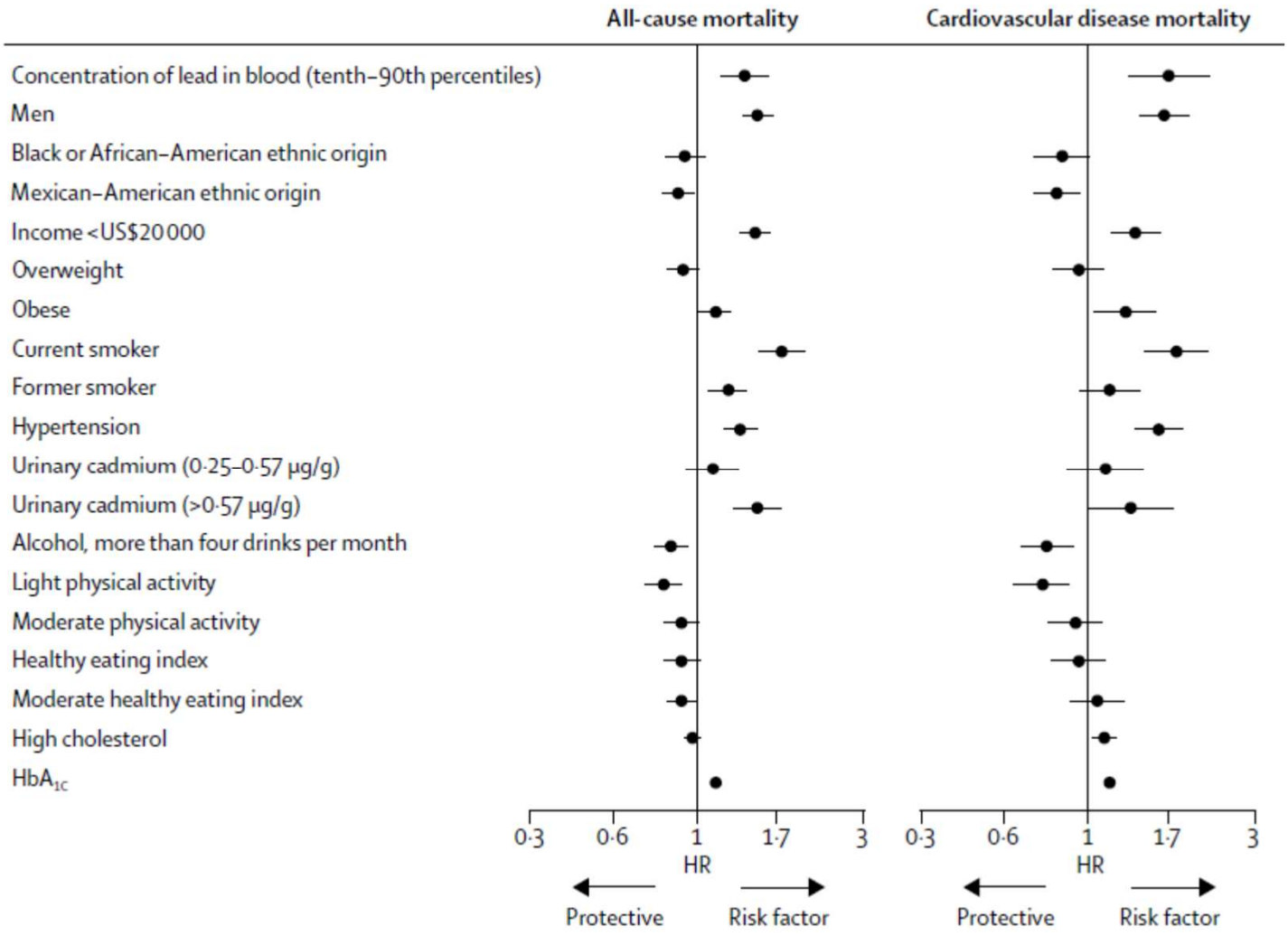
- Based on epidemiology studies
  - Subsequent analyses of NHANES cohort (blood)
  - Normative Aging Study (bone)



HR of IHD in NHANES-III
Adjusted for age, sex, income, ethnicity, BMI, smoking status, alcohol, physical activity, cadmium in urine

Lanphear et al., 2018

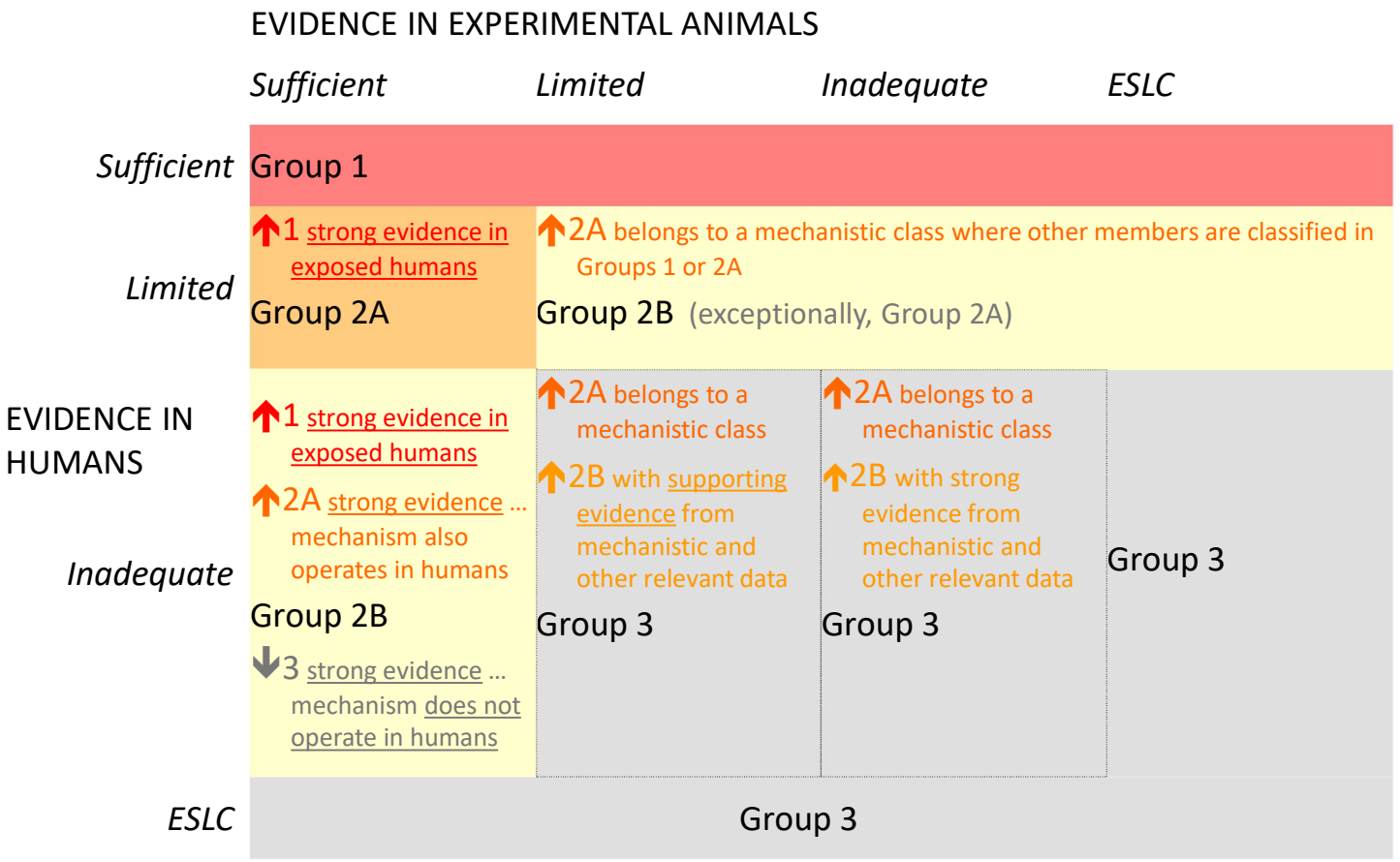
Blood lead vs. other risk factors – NHANES-III



Integration of epidemiology with other lines of evidence

- All evaluation and classification schemes recognized the importance of human data
  - clinical and epidemiological studies, rarely intervention studies
- However, approaches are heterogeneous in weighting and integrating the various lines of evidence

IARC (Hazard Identification)



ECHA

- In integrating the available evidence, human data of good quality are particularly valuable (i.e. they are given preference or more weight than other data) because:
  - they apply directly to humans
  - the data are more likely to have been obtained from exposure conditions relevant to workers

SCOEL

- Studies can be case reports and epidemiological studies or experimental studies. Further, data may be derived from in silico modelling
- Studies sorted by:
  - study design
  - model used
  - type of evidence provided

Evidence of prevention of occupational risk

- The best epidemiology evidence on temporal changes of occupational risk is an analysis by *time of first employment* (preferably adjusted for other characteristics of exposure)
  - Results from individual cohorts vs. population data
  - Interpreted as ‘early stage’ mechanisms
- Examples:
  - Nickel smelting (cohort)
  - Vinyl chloride production (cohort)
  - Mesothelioma (population data)
- Role of EOL vs other factors

Temporal trends in nickel exposure level

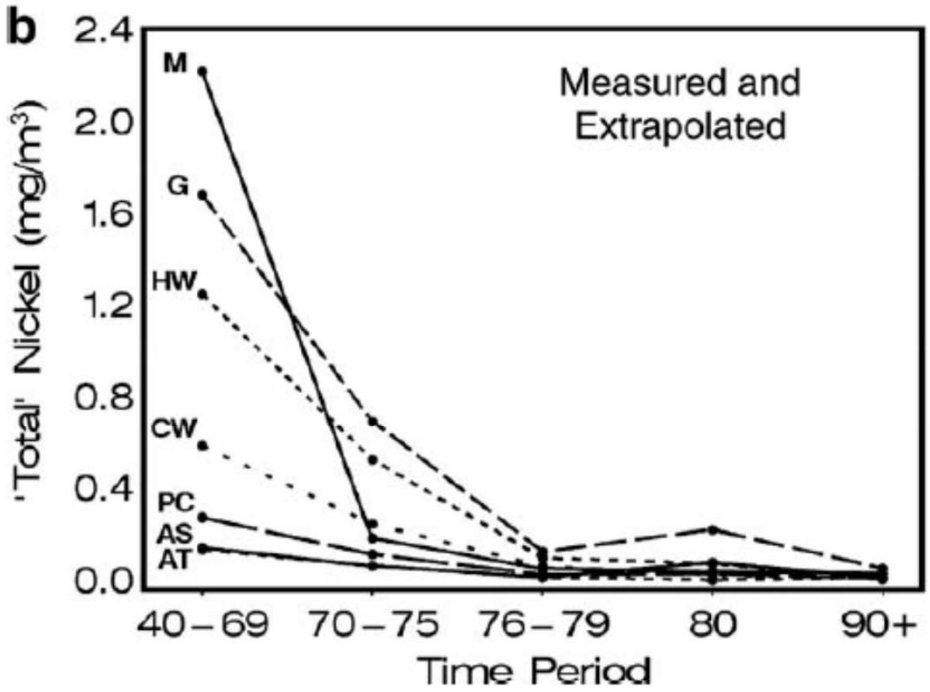
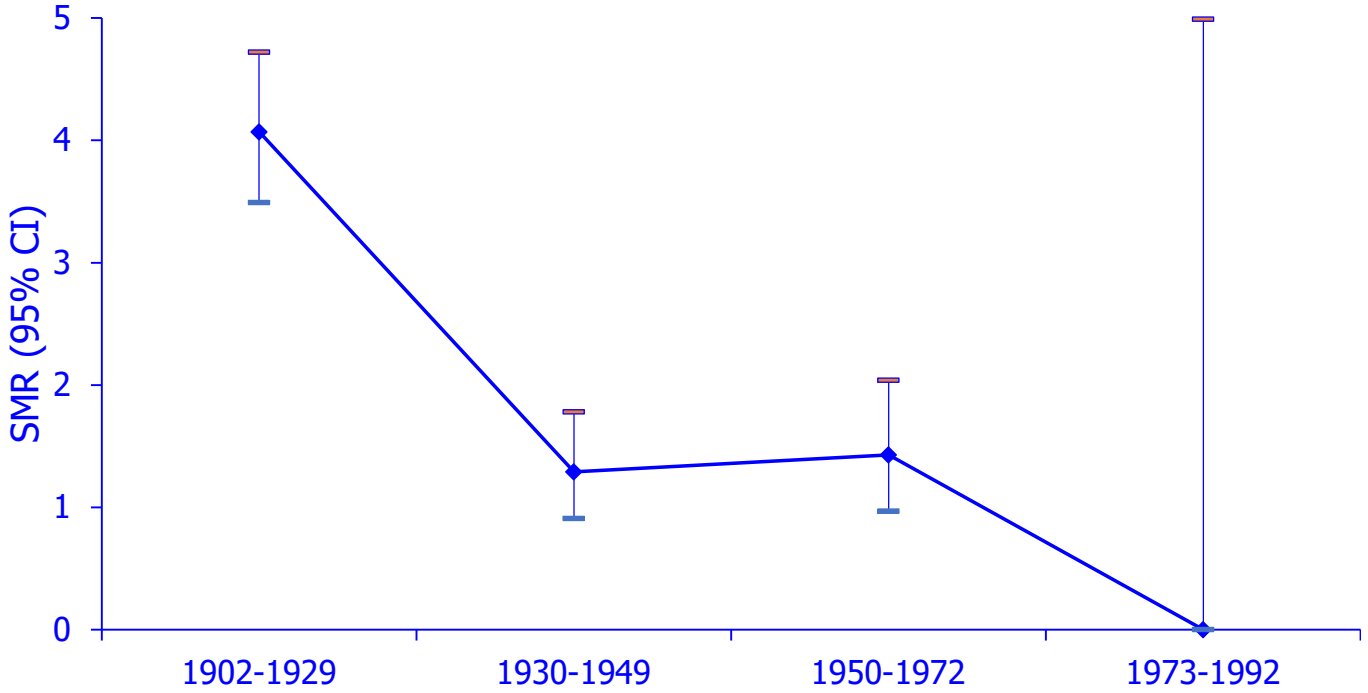
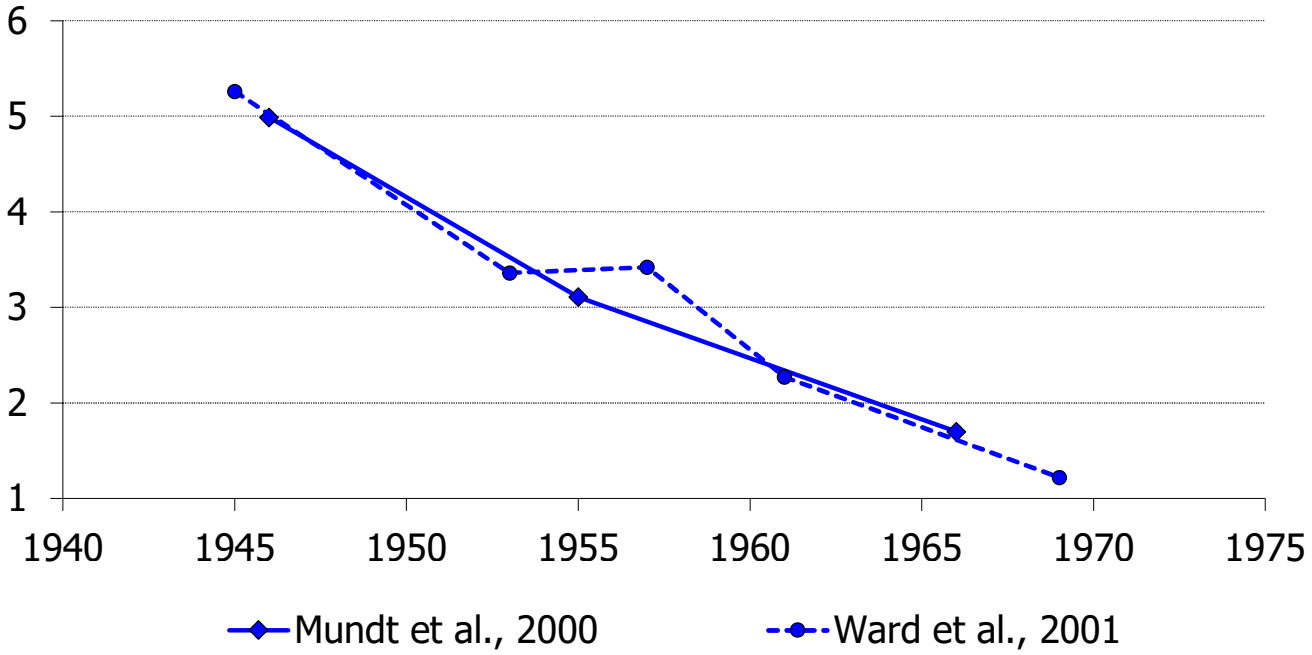


Fig. 1. (a) Measured and (b) measured and extrapolated average 'total' nickel concentrations (mg/m^3) for work areas in nickel alloy production, 1940 – present: M, melting; G, grinding; CW, cold working; HW, hot working; PC, pickling and cleaning; AT, administrative and technical; AS, allocated services.

SMR of lung cancer among Clydach nickel refinery workers by year of hire



SMR of liver cancer in two cohorts of VC exposed workers



Boffetta et al., 2003

Neoplastic vs. non-neoplastic effects

- Some regulatory committees (e.g., DECOS and ECHA's RAC) have based OELs for carcinogens on the occurrence of non-carcinogenic endpoints of the haematopoietic system and the occurrence of chromosome-based genotoxicity

- In the case of **benzene**, these agencies judged that any risk from carcinogenicity would be adequately controlled by complying with limits based on non-neoplastic effects

DECOS

- The Health Council of the Netherlands established a new occupational standard of 0.2 ppm / 8 h for benzene in 2014
- DECOS considered that measured concentrations were similar to those experienced before sampling
- DECOS used air level reported by Lan et al. (2004) – 0.57 ppm and applied a safety factor of 3

ECHA

ECHA based their 2018 recommended OEL on effects other than cancer, specifically genotoxicity

Their recommendation of 0.05 ppm/8 h is substantially lower than most other proposed standards

RAC stated that there is now sufficient evidence available to set a MOA-based threshold for benzene

History of introduction of OEL – the case of benzene

- In the first 50 years since the first reported case of benzene-associated leukemia, benzene has been neither widely acknowledged nor uniformly controlled as a carcinogen in the US
- Delays in controlling benzene as a carcinogen has resulted primarily from the reluctance of industry and Government to accept the accumulated case-reports and epidemiological observations as scientific evidence of the leukemogenic properties of benzene

Early reports of benzene poisoning

- 1862 Greenburg – benzene poisoning (exposure up to 1%, or 10,000 ppm); cases of anaplastic anemia
- 1897 LeNoir and Claude – case report associated exposure to benzene with leukemia
- 1897 Santesson – animal experiments in which rabbits are exposed to benzene had the hematological effects observed in humans
- 1910 Selling, 1922 Hamilton – case reports of benzene intoxication, some with a fatal outcome, with hematotoxicity with leucopenia
- 1916 Selling, 1920 Weiskotten et al. – more definitive animal experiments

The first cases of “benzene leukemia”

- 1928 - Delore and Borgomano described a case of acute leukemia in a group of workers so heavily exposed that none could stand more than 2 months without falling ill
- Shortly after this first description, other cases of leukemia attributed to benzene were reported
- 1932 - Lignac succeeded in producing various types of leukemia in mice

Chronology of recommended benzene concentrations in workplaces in USA

Year	Concentrations (ppm)
1941	100 MAC
1947	50 8hTWA
1948	35 8hTWA
1957	25 8hTWA
1963	25 Ceiling
1969	10 8hTWA
1971	10 8hTWA

The settings of benzene OEL over time by ACGIH

Year	OEL (ppm, 8-h TWA)	Authority
1946	100	ACGIH
1947	50	ACGIH
1948	25	ACGIH
1977	10	ACGIH
1997	0.5	ACGIH

Historical overview of OEL setting by other authorities

Year	OEL (ppm, 8-h TWA)	Authority
1948	<50	API
1957	25	API
1964	25	DFG
1967	25	UK
1973	10	USA OSHA
1979	8	DFG
1985	10	Netherlands
1988	5	UK
1991	5	DFG

Year	OEL (ppm, 8-h TWA)	Authority
1994	2.5	DFG
1994	2.3	Netherlands
1996	1	USA OSHA
1997	1	EU SCOEL
2000	3	UK
2003	1	DFG
2003	1	UK
2014	0.2	Netherlands
2018	0.05	EU RAC

1976 The first cohort study of workers exposed to benzene

- Employees involved in the manufacture of ‘‘Pliofilm,’’ a rubberized food wrapping material, at the Goodyear Tire and Rubber Company manufacturing facilities located in Akron and St. Marys, Ohio, and occupationally exposed to benzene in 1940-49 were followed for vital status up to 1975
- In comparison with two control populations, a significant ($p<0{\cdot}002$) excess of leukemia was observed.
- Almost immediately upon the release of the results, the US Department of Labor issued an Emergency Temporary Standard to reduce benzene exposure in the workplace to 1.0 ppm, determined to be the lowest feasible level following OSHA policy at the time for carcinogens

1976 The first cohort study of workers exposed to benzene

Causes of death (ICD codes)	Benzene-exposed workers		Comparison group	SMR
	Deaths observed	Deaths expected		
All causes	140	187.5809	(u.s.w.m)	75
(200-205)	9	3.4497	(u.s.w.m)	260 £
204	7	1.3831	(u.s.w.m)	506 ¥
(200-205)	9	5.102	(F.G.)	176
204	7	1.4758	(F.G.)	474 ¥

ICD 7th Revision Codes

(200 – 205) Total lymphatic and haematopoetic cancer

(204) Leukemia only

£p<0.05

¥p<0.02

SMR = observed/expected x 100

Evidence-based identification of OEL for an occupational carcinogens – example of benzene

(a) Systematic review of hematological and genotoxic studies

(b) Classify such studies with regard to epidemiological quality criteria

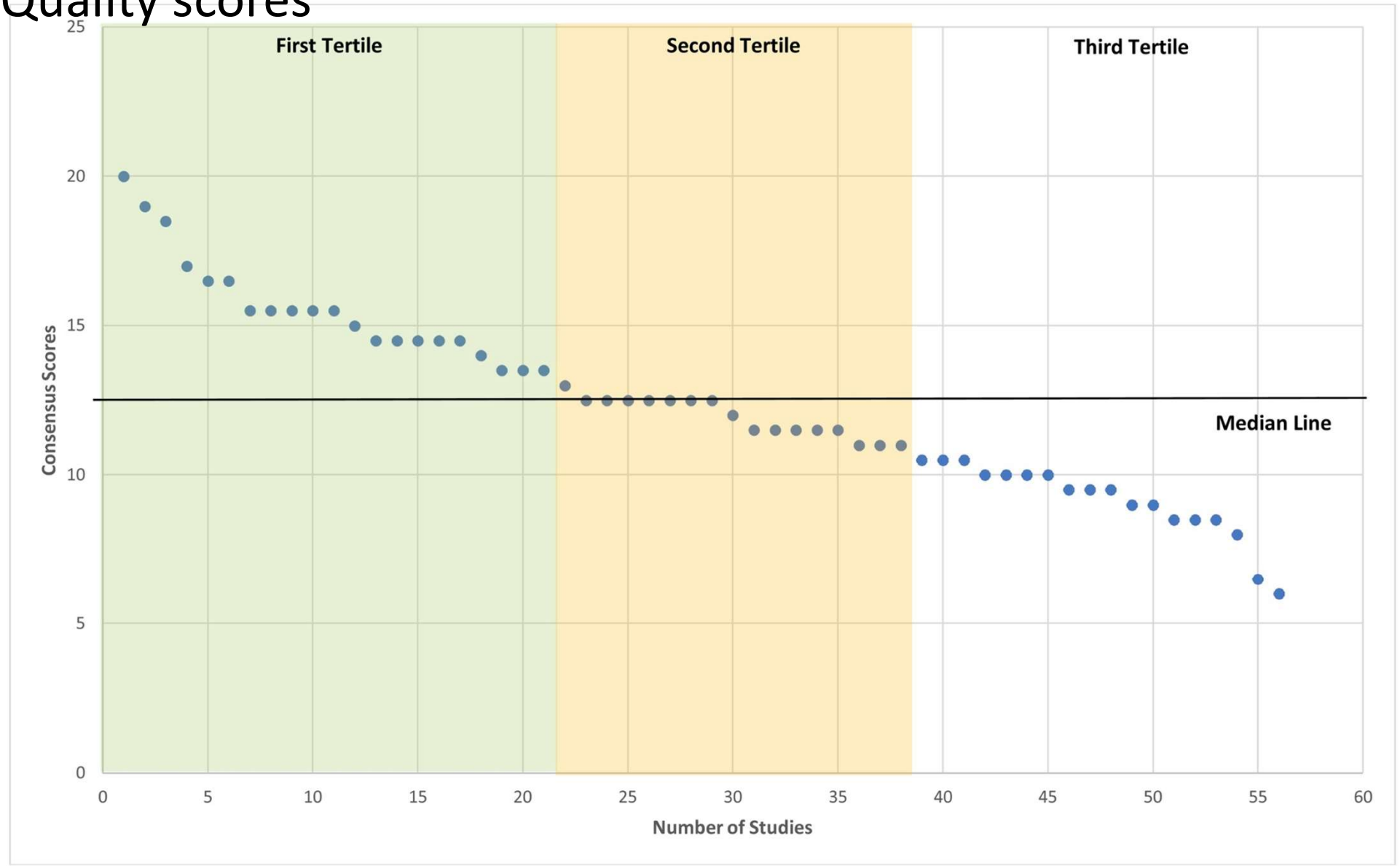
(c) Identify unique study populations; select the highest quality studies

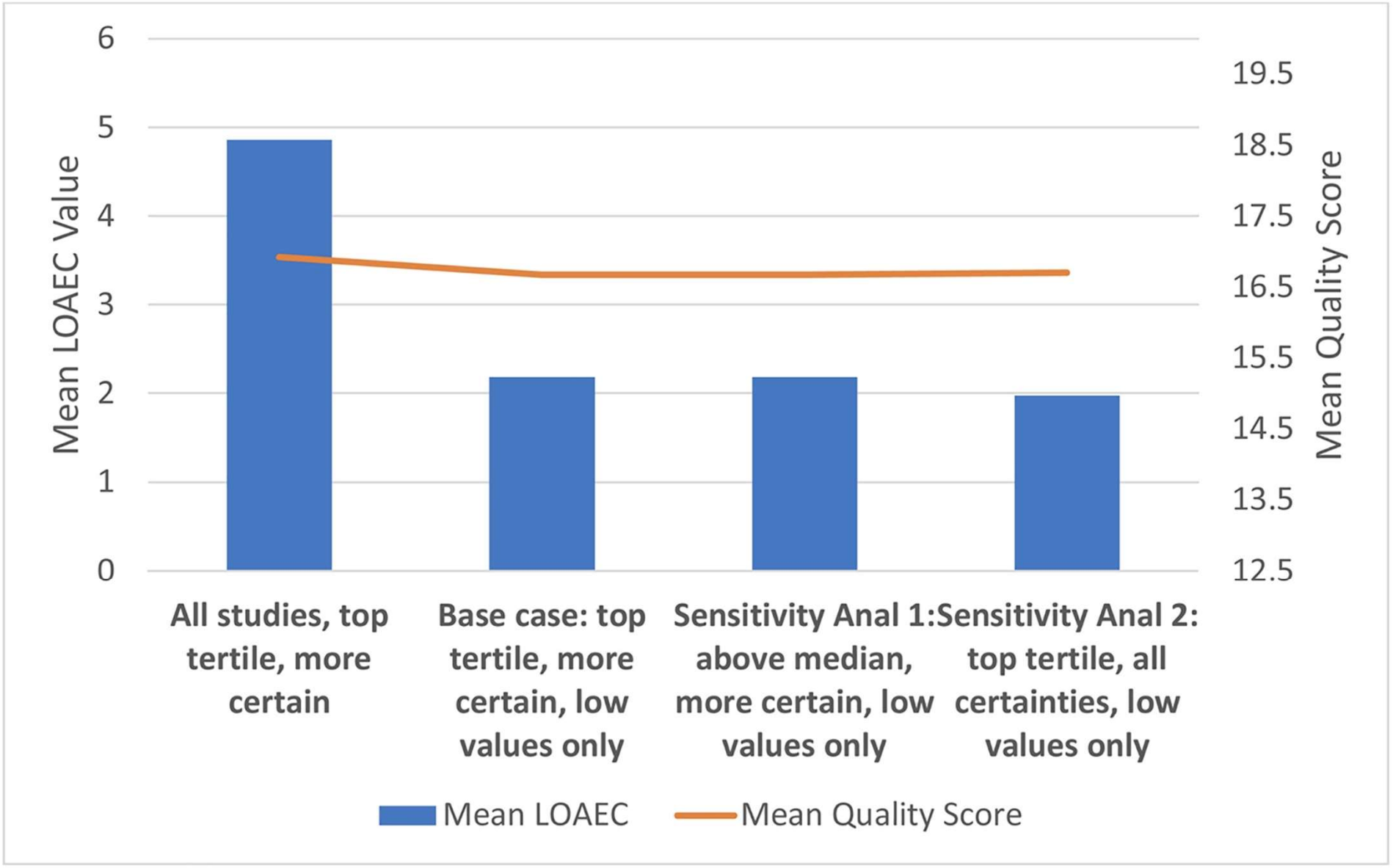
(d) Select Lowest Observed Adverse Effect Concentrations (LOAECs) and No Observed Adverse Effect Concentrations (NOAECs)

(e) Classify LOAECS and NOAECs with respect to certainty

Schnatter et al., 2020

Quality scores




6
5
4
3
2
1
0
Mean LOAEC Value
19.5
18.5
17.5
16.5
15.5
14.5
13.5
12.5
Mean Quality Score
All studies, top tertile, more certain
Base case: top tertile, more certain, low values only
Sensitivity Anal 1: above median, more certain, low values only
Sensitivity Anal 2: top tertile, all certainties, low values only
Mean LOAEC
Mean Quality Score

Result of evidence-based assessment

For both haematotoxicity and genotoxicity, best quality studies support effects at 2 ppm (8 h TWA) or higher and no effects at 0.5 ppm (8 h TWA) and lower.

Applying an assessment factor of 4 to the LOAEC of 2 ppm would give a NOAEC of 0.5 ppm (2 for dose-response and 2 for interspecies extrapolation).

The use of peripheral blood measures of bone marrow effects introduces some scientific uncertainty, thus an extra assessment factor of two is applied.

An OEL of **0.25 ppm** (8 h TWA) for benzene is the best estimate based on available human data.

Schnatter et al., 2020

Benzene OEL - Conclusions

The OELs for benzene have been lowered over more than 2 orders of magnitude since the first value of 100 ppm to **0.05-0.25 ppm.**

Results from epidemiology have been instrumental in this process.

It is possible to use evidence-based approaches to derive OEL.

Accurate determination of dermal as well as low/intermittent airborne

exposure remains an issue; biomonitoring may offer a solution

- Urinary S-PMA seems to be the most promising biomarker for the assessment of low-level
- Proper validation of urinary S-PMA is currently lacking

Conclusions

- Although epidemiology studies impact on OEL setting, a formal assessment is complicated by:
  - Latency in regulatory decisions
  - Heterogeneity between countries and organizations
  - Heterogeneity in combining lines of evidence
- Evidence is stronger for carcinogenic than non-carcinogenic agents.
- The discipline of risk assessment has matured, and input from epidemiology has played a key role in it.

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  - Toxic Substance Research Program, Department of Defense
  - Horizon Europe, European Commission

Acceptable Risk – Practical Considerations

- Safety practitioners should accept that zero risk is not attainable for hazards that cannot be eliminated.
- Where hazards cannot be eliminated, the goal should be to reduce risks so that the residual risks are acceptable.
- Safety practitioners should debate and consider accepting the proposed definitions for terms defined herein.
- Risk assessments and the risk decision process should become more structured and documented. This process will advance the understanding and acceptance of the concept of acceptable risk and of residual risks
- Safety practitioners should recognize that a universal definition of an acceptable risk level cannot be attained because of the many variables in individual risk situations

‘Significant’ risk

- OSHA utilizes the guidance provided by the U.S. Supreme Court and considers a risk of 1-in-1000, for a working lifetime, as significant (i.e., unacceptable) and necessitating some sort of regulatory action
- ACGIH has no stated policy regarding ‘significant risk’; TLVs are set at values that are “believed” to be protective of “nearly all workers”
  - TLVs are typically set based on ‘no observed effect’ concentrations reported in the literature or at levels where the risk does not significantly exceed that seen in unexposed workers
- Use of statistical significance has been criticized because it depends on the power of the underlying studies

1976 The first cohort study of workers exposed to benzene

- Retrospective cohort study
- All white men (n = 748) who had direct exposure to benzene between 01/01/1940 and 31/12/1949
- Follow-up of all study-cohort members was attempted from first employment to 30/06/1975
- Vital status has been determined for approx.75% of the 748 cohort members; 25% were assumed to be alive to avoid overestimating the true risk of lymphatic and haemopoietic malignance associated with benzene exposure
- Causes of death were determined from death certificates and were coded according to ICD (converted to ICD 7 th revision)

1976 The first cohort study of workers exposed to benzene

- Person-years of observation and causes of death were determined from 01/01/1950 to 30/06/1975, those occuring before 01/01/1950 were excluded from analysis since vital statistics on lymphatic and haemopoetic malignancies were not published before that date
- Two populations were chosen as control groups for generating the numbers of expected deaths in the study population
- The 1st group consisted of the U.S. White male general population standardised for age and time period over which the study cohort lived
- The 2nd group consisted of 1447 White men who had been employed in Ohio at a fibrous-glass construction-products factory between 01/01/1940 and 31/12/1949, and who had achieved 5 or more years of employment by 01/06/1972 (cut-off date for vital status ascertmainment)

1976 The first cohort study of workers exposed to benzene

Results:

- 140 observed deaths from all causes among benzene-exposed workers compared with 187.6 expected deaths (incomplete follow-up of the study population)
- Significant excess of deaths from malignancy of the lymphatic and haemopoietic systems compared to that expected on the basis of death-rates of U.S. White males
- Five-fold elevation in the risk of leukemia in general and an approximately 10-fold elevation in the risk of myelomonocytic leukemias
- The period between initial exposure and death ranged from 2 to 21 years.

1976 The first cohort study of workers exposed to benzene

Case, N	Type of leukaemia	Age at death (year)	Period of initial exposure to death (year)
1	Acute myelogenous	60	13
2	Acute myelogenous	65	10
3	Acute myelogenous	62	21
4	Acute myelogenous	57	19
5	Monocytic	57	15
6	Chronic myelogenous	29	2
7	Monocytic	36	17
8	Myelogenous	28	3

Infante PF, Rinsky RA, Wagoner JK, Young RJ. Leukaemia in benzene workers. Lancet. 1977 Jul 9;2(8028):76-8. doi: 10.1016/s0140-6736(77)90074-5. PMID: 69157.