

# Science to Inform Classification & Regulation of PAH-Containing Substances

What Does the Science Say About Hazard Classifications in  
PAH-Involved Industries?

Anne LeHuray

ACCCI Meeting  
Bonita Springs, FL  
April 28, 2019

# The last time I spoke to this group.... .....May 2013

- Topics: ACCCI is an Associate Member of
  - Naphthalene Council
    - 2013 - Naphthalene Research Program was winding down
    - Now – Research program is complete, the next step is EPA's
  - Pavement Coatings Technology Council
    - 2013 - “WHEN GOVERNMENT SCIENTISTS USE THE PLATFORM & RESOURCES OF THE US GOVERNMENT TO TARGET COAL TAR FOR EXTINCTION”
    - Now – Proposed bans continue be introduced in towns, cities, counties, and states; PCTC continues to oppose; ACCCI continues to help

# Regulating Carcinogens

- Laws & Regulations around the world often REQUIRE treating substances as carcinogens if listed as carcinogens or potential carcinogens by:
  - United Nations World Health Organization - IARC (classification 1, 2A or 2B)
  - US Report on Carcinogens (Known or Reasonably Anticipated to be a Human Carcinogen)
- Naphthalene
  - Currently listed as IARC 2B and US RoC “reasonably anticipated”
  - Key findings of research program
    - Multiple ways primates and rodents process naphthalene differently
    - Studies in rats & mice aren't relevant to assessing human cancer risk
    - Naphthalene not likely to be a human carcinogen at typical environmental or current occupational exposure levels
  - Subject to 3 EPA programs: FIFRA, IRIS, and now a TSCA priority



# PAH-containing substances & PAH-involved industries

Worldwide regulations are based on science that is 50  
years out of date

# PAHs – The Regulatory Science Dilemma

- Chemically isolated individual PAHs arguably...
  - The most commonly found chemicals in routine analysis of *solid* phase environmental samples (soil, sediment, air particulates; but *not* water or most biological samples)
  - The most toxicology studies of any chemical of environmental concern
  - Some (not all) individual PAHs cause tumors in rats & mice

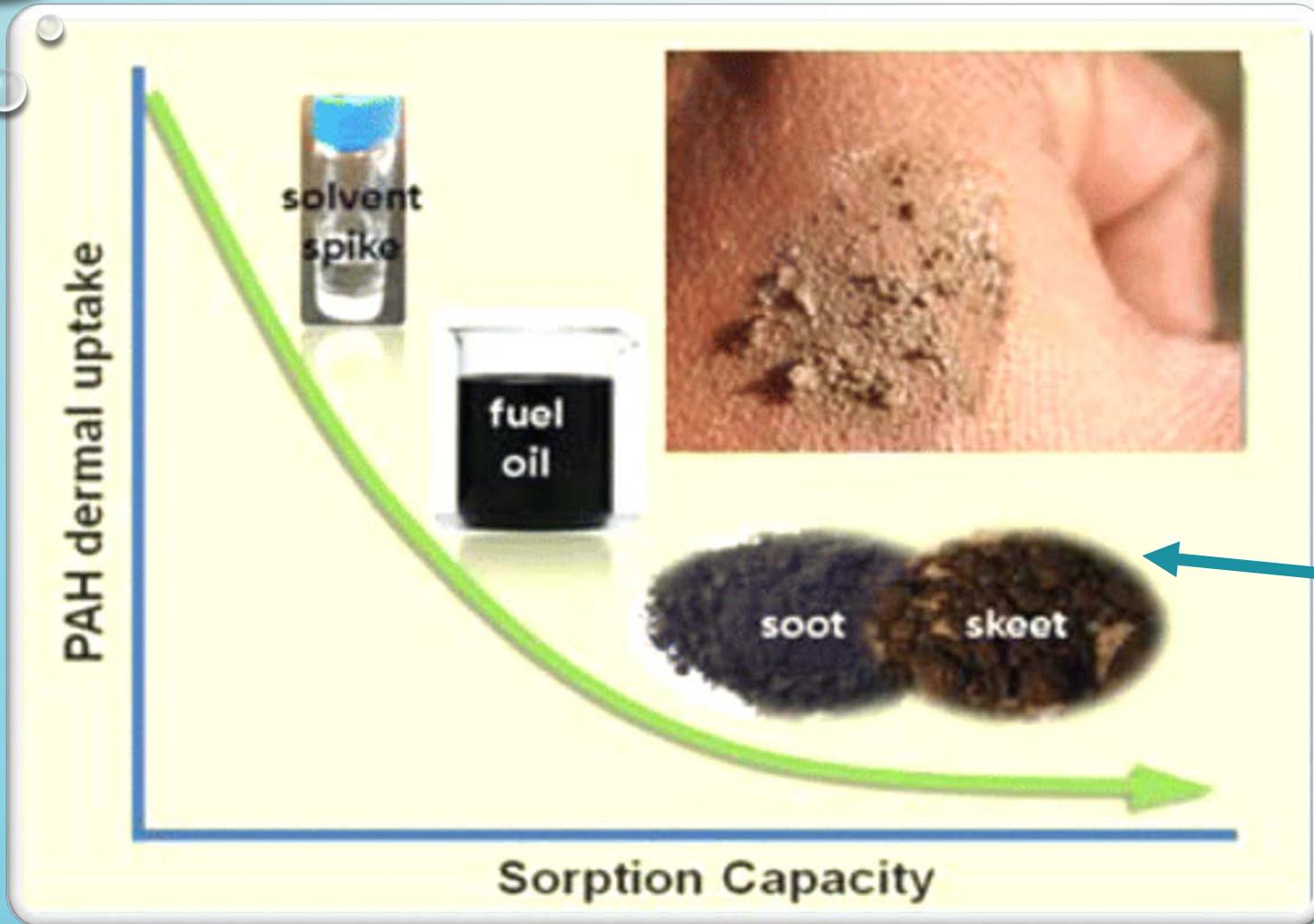
**BUT**

- In the real world, virtually no one – animal or vegetable – is exposed to chemically isolated individual PAHs

# This makes a difference because....

- PAHs occur as mixtures containing dozens or hundreds of individual PAH compounds
- PAHs are not commonly separated for commercial purposes there is virtually no exposure to individual PAHs by any creature outside toxicology laboratories
- Exposures are to different substances that contain variable mixtures of PAHs combined with a variety of other organic and inorganic compounds
- Studies of individual PAHs present in a mixture gives no information about biochemical interactions
  - synergism or antagonism or bioavailability
- Different PAH-containing materials are known to behave differently in biological systems

bioavailability & absorption varies with source of PAHs



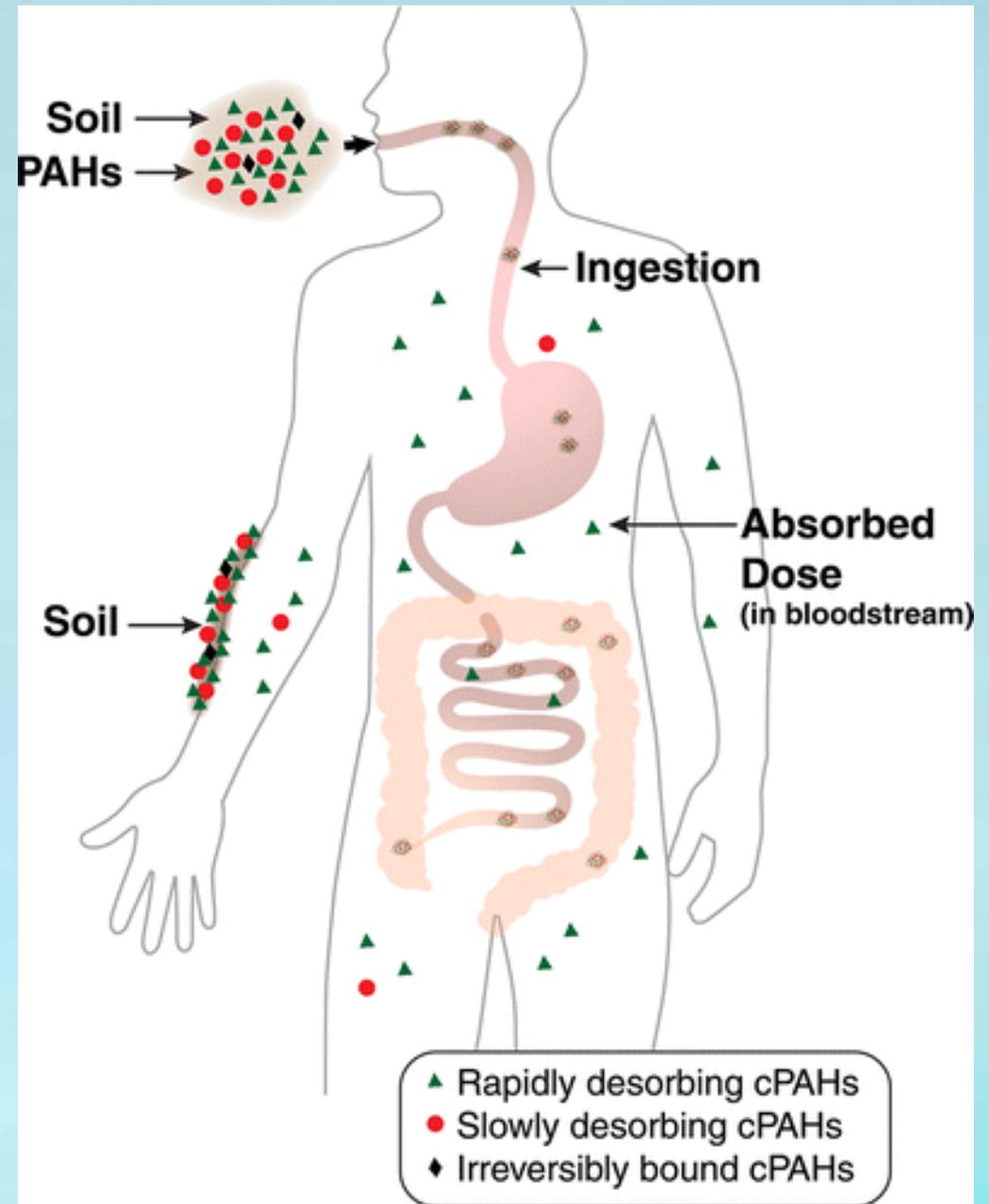
Coal Tar Pitch is *least* readily absorbed

Xia *et al.*, 2016

## Bioavailability & Absorption Studies

### Coal Tar Pitch

- *Slowly absorbing cPAHs*
- Very low PAH absorbed (in bloodstream)
- Higher percentage of *irreversibly bound cPAHs* than any other matrix studied

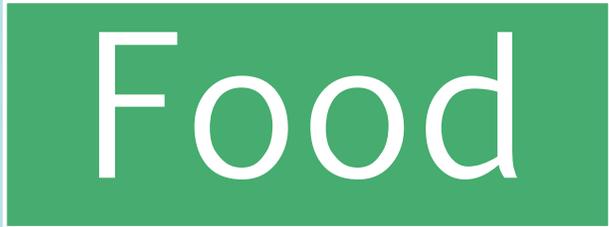


## Polycyclic Aromatic Hydrocarbons in Food<sup>1</sup>

### Scientific Opinion of the Panel on Contaminants in the Food Chain

(Question N° EFSA-Q-2007-136)

Adopted on 9 June 2008

A green rectangular box with a white border containing the word 'Food' in a large, white, sans-serif font.

## SUMMARY

Polycyclic aromatic hydrocarbons (PAHs) constitute a large class of organic compounds that are composed of two or more fused aromatic rings. They are primarily formed by incomplete combustion or pyrolysis of organic matter and during various industrial processes. PAHs generally occur in complex mixtures which may consist of hundreds of compounds. Humans are exposed to PAHs by various pathways. While for non-smokers the major route of exposure is consumption of food, for smokers the contribution from smoking may be significant. Food can be contaminated from environmental sources, industrial food processing and from certain home cooking practices.

**Table 2:** Maximum levels (MLs) for benzo[*a*]pyrene as laid down in Regulation (EC) No. 1881/2006. See the original Regulation for further definitions and explanations of individual food commodities.

Foodstuff	ML (µg/kg wet weight)
Oils and fats (excluding cocoa butter) intended for direct human consumption or use as an ingredient in foods	2.0
Smoked meats and smoked meat products	5.0
Muscle meat of smoked fish and smoked fishery products, excluding bivalve molluscs. The maximum level applies to smoked crustaceans, excluding the brown meat of crab and excluding head and thorax meat of lobster and similar large crustaceans ( <i>Nephropidae</i> and <i>Palinuridae</i> ).	5.0
Muscle meat of fish, other than smoked fish	2.0
Crustaceans, cephalopods, other than smoked. The maximum level applies to crustaceans, excluding the brown meat of crab and excluding head and thorax meat of lobster and similar large crustaceans ( <i>Nephropidae</i> and <i>Palinuridae</i> )	5.0
Bivalve molluscs	10.0
Processed cereal-based foods and baby foods for infants and young children*	1.0
Infant formulae and follow-on formulae, including infant milk and follow-on milk*	1.0
Dietary foods for special medical purposes intended specifically for infants*	1.0

\*The maximum level applies to the product as sold.

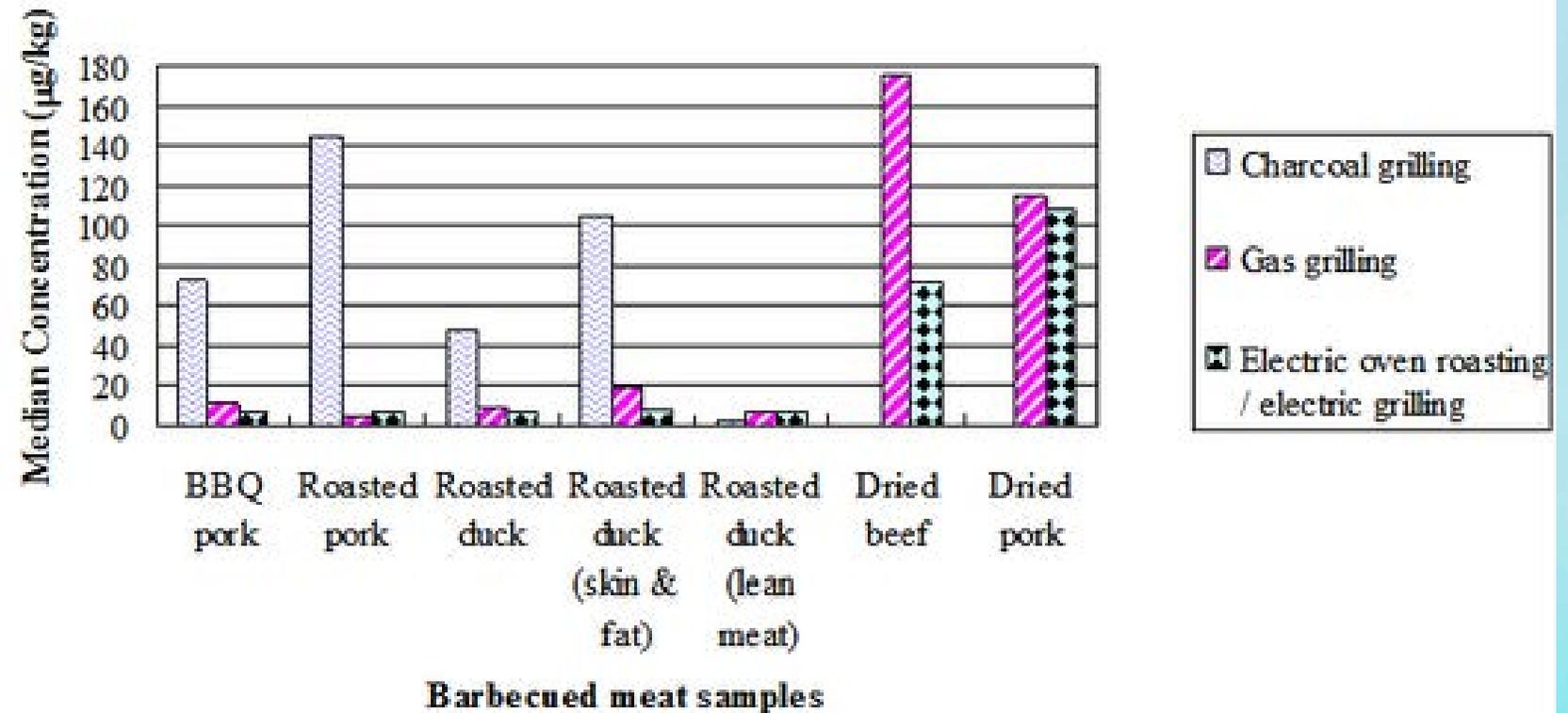
# EU B(a)P limits

No restrictions on cooking methods that result in PAH formation:

- Barbecue
- Grilling
- Smoking
- Toast
- Searing

# Hong Kong Centre for Food Safety Study of PAHs in BBQ Meat

Figure 4: Median Concentration for Total PAHs in Barbecued Meat Samples



Overwhelmingly exposure to PAHs is via food

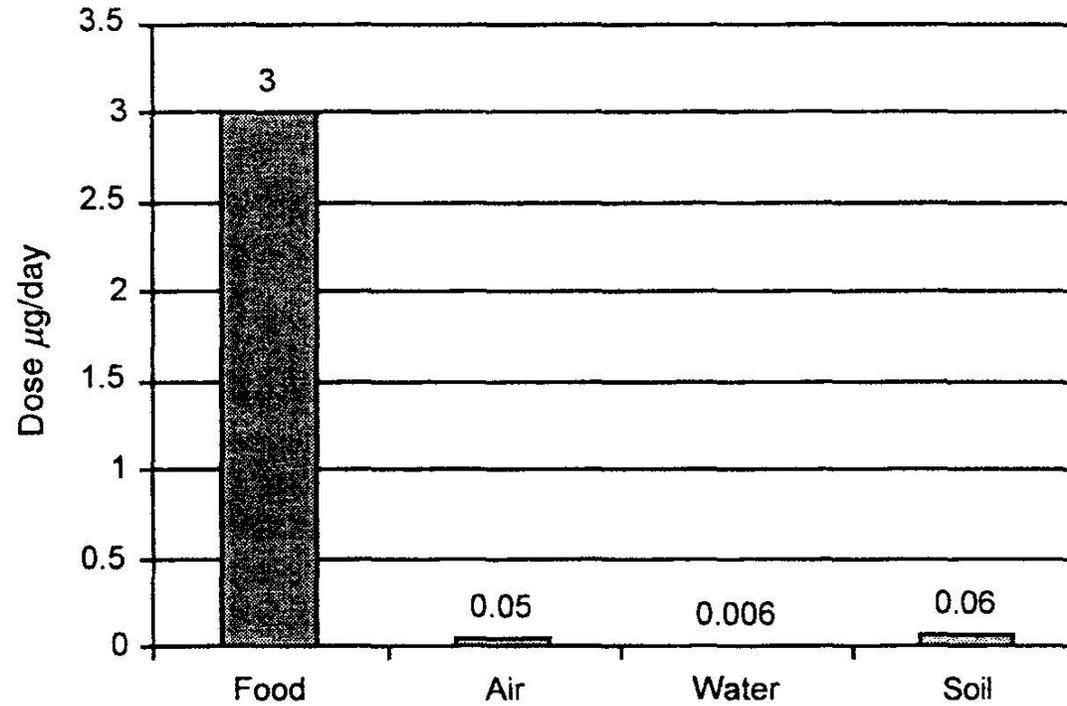
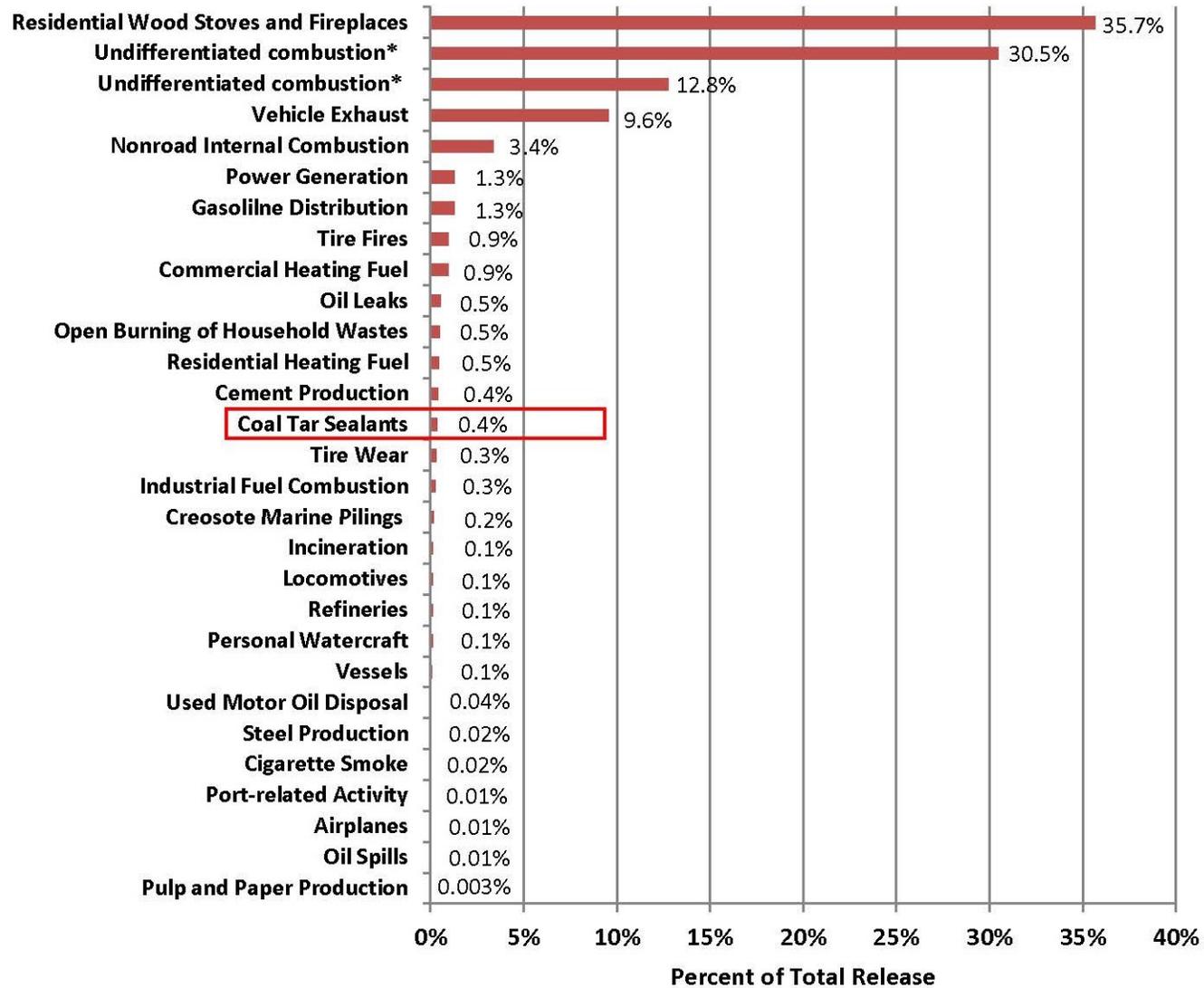


Figure 5-1. Relative Doses of Carcinogenic PAHs  
Source: Menzie *et al*, 1992

## Total PAH Release Within the NY/NJ Watershed

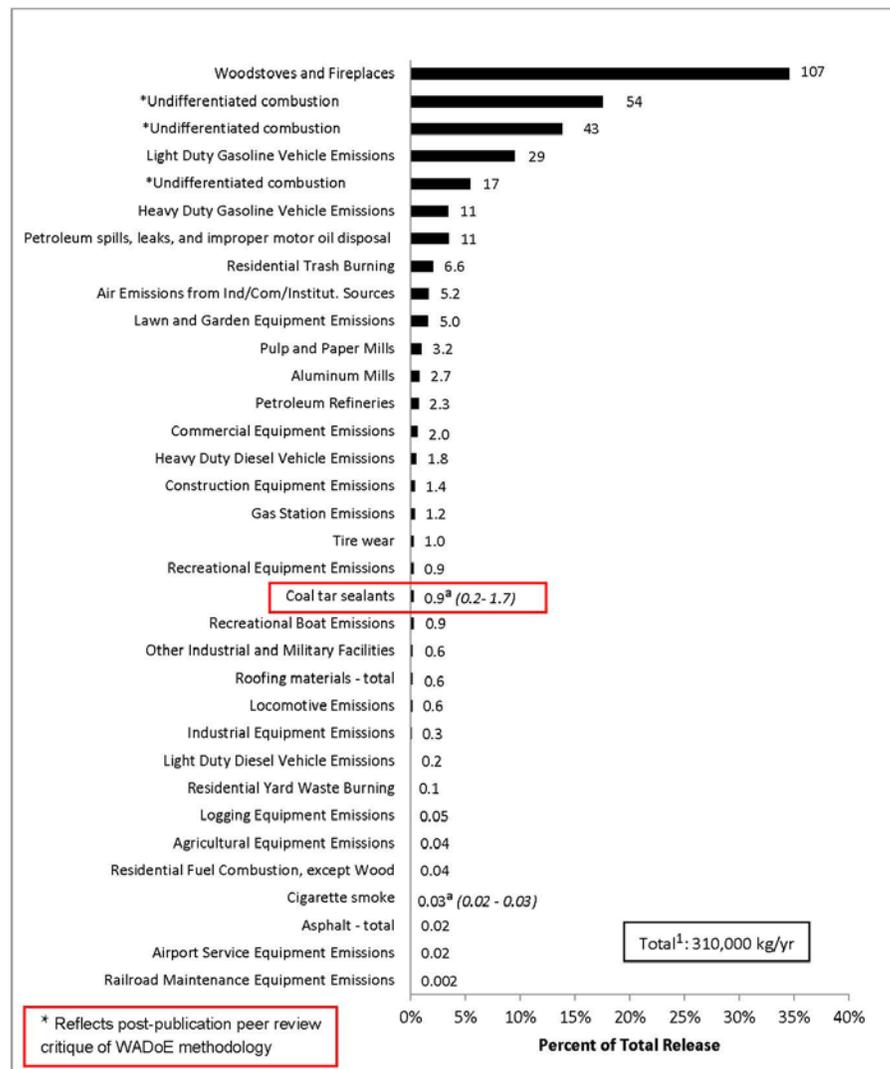
(Source: New York Academy of Sciences, 2007)



\* Reflects post-publication peer review critique of NYAS methodology.

PAHs in  
Sediment  
NY Harbor

# PAHs in Sediment Puget Sound



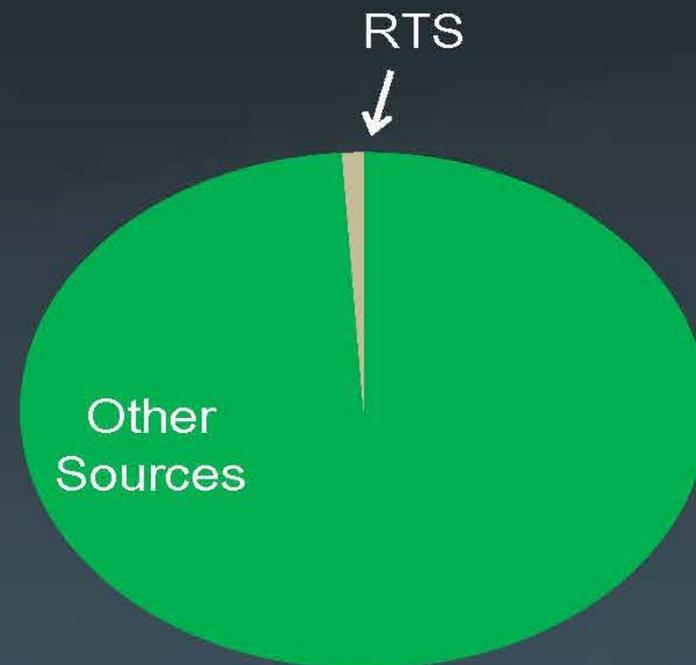
<sup>1</sup>Sum of best estimates. Best estimates are either the mean, mid-point, median, or most reasonable estimate for each source.

<sup>a</sup>Mid-point of range

Figure 31. Total PAH Release in the Puget Sound Basin (values shown are thousands kg/yr).

# Evidence Suggests Other Sources of PAHs are More Important Than Refined Coal Tar Sealants (RTS)

- The model used by the USGS indicates the PAH contribution of sealed parking lots is no greater than unsealed lots.<sup>1,2</sup>
- The model indicates RTS is not an important source of PAHs.<sup>1,2</sup>
- Independent evaluations indicate RTS is not an important source.<sup>3,4</sup>

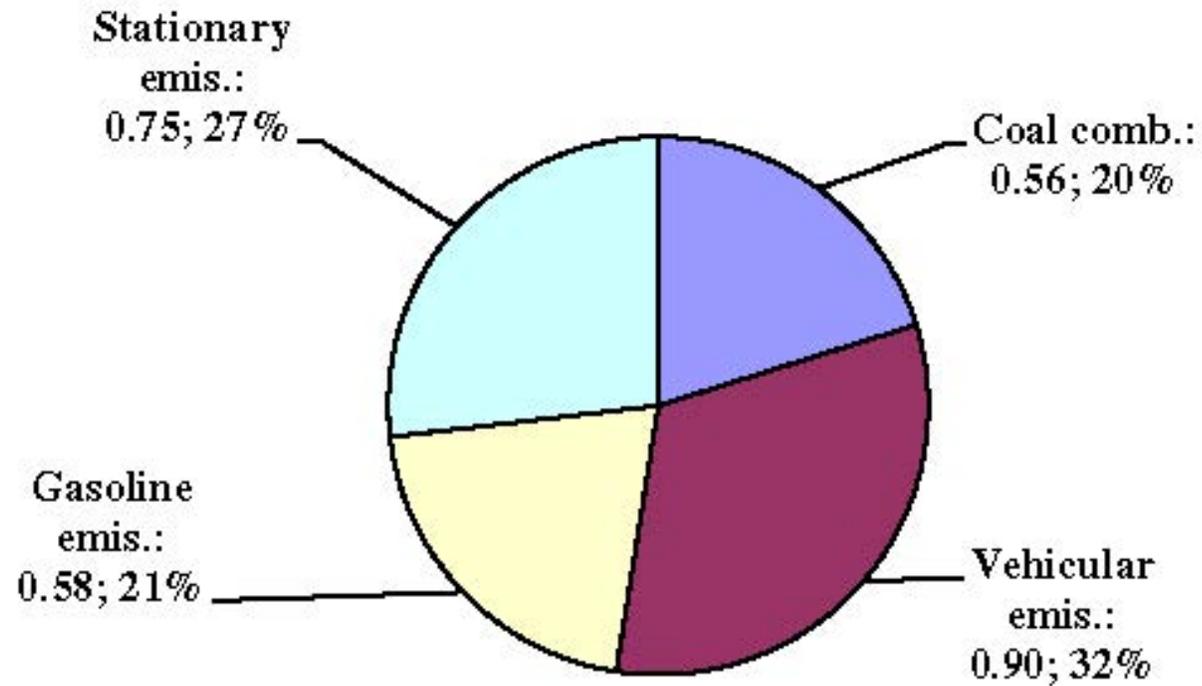


1. O'Reilly. 2015 Arch Env Contam Toxicol. 68:1.
2. O'Reilly & Ahn. 2017. Env Tox Chem. In press.
3. Zou et al. 2015. Env Pollution. 205:394.
4. WDOE. 2011. Report 11-03-055.

# Sources of PAHs in Atmospheric particulates Zaragoza City, Spain

**b**

**Cold season**



# Pharmaceutical Uses

## Clinical

- Over-the-counter (non-prescription)
- FDA: Coal tar is safe & effective for use OTC medicine for skin conditions
    - Dandruff
    - Psoriasis
    - Eczema
    - Coal Tar Soap
  - Up to 5% coal tar



Patient undergoing coal tar application  
as part of Goeckerman treatment.

Photo courtesy of the University of Michigan Health System

## Is RTS based on a “hazardous waste?”

- RTS is based on RT-12, a selectively refined fraction, from coke oven byproduct crude coal tar
- By rule, coke oven CT is a byproduct, not a hazardous waste (EPA/530-F-92-013)
- By litigation, CT not a hazardous waste UNLESS it fails TCLP (Association of Battery Recyclers, Inc., et al. v. US Environmental Protection Agency (April 21, 2000))
- EPA Opinion Letter (RCRA Online 14492)
- Not subject to federal Land Disposal Restrictions

# Regulating Carcinogens

- Laws & Regulations around the world often REQUIRE treating substances as carcinogens if listed as carcinogens or potential carcinogens by:
  - United Nations World Health Organization - IARC (classification 1, 2A or 2B)
  - US Report on Carcinogens (Known or Reasonably Anticipated to be a Human Carcinogen)
- Both are “hazard assessments”

# How are Hazard Assessments Performed (currently)

Evaluations of 4 types of data. For PAH-containing substances, evaluation of exposure to real world whole mixtures, but toxicology of individual PAHs

1	Exposure Data	Real-world human exposures to and evidence of cancer in humans associated with complex mixtures of PAH compounds within materials that also contain non-PAH substances
2	Cancer in Humans	
3	Cancer in Experimental Animals	Rely almost exclusively on studies of synthetically isolated PAH compounds in laboratory models rather than studies of the PAH mixtures
4	Other Relevant Data	

**Table 1. IARC monographs that include human exposure information via occupational exposure studies in industrial processes involving PAH-containing substances. Typically, the latest IARC monograph volume in which exposure studies in an industry are discussed supersede previous volumes.**

IARC Monograph Volume (Year)	IARC Group	3 (1973)	33 (1984)	34 (1984)	35 (1985)	Supplement 7 (1987)	92 (2010)	100F (2012)
<b>Occupational Exposure Industry</b>								
Aluminum production	1			X		X	X	*
Bitumen (occupational exposure)	2B				X	X		
Carbon black	2B	X	X			X		
Carbon electrode manufacturing	2A						X	
Coal gasification	1			X		X	X	
Coal tar distillation	1	X			X	X	X	*
Coal tar pitch	1	X				X		X
Coke production	1			X		X	X	*
Creosote	2A					X	X	
Iron and steel founding (occupational exposure during)	1			X		X		
Mineral oils (untreated or mildly treated)	1	X	X			X		X
Shale oils	1				X	X		X
Soot (as found in occupational exposure of chimney sweeps)	1	X			X	X	X	X

IARC Group 1: Carcinogenic to humans

IARC Group 2A: Probably carcinogenic to humans

IARC Group 2B: Possibly carcinogenic to humans

X - Human exposure studies evaluated or cited

\* - New laboratory data, but no new human exposure studies evaluated

Classifications  
all based on

- Skin cancer  
or
- Lung cancer

# Skin Cancer

**Table 2. Summary of IARC Skin Cancer Hazard Classifications for Occupations Involving PAH Mixtures**

Mixture or Occupation	IARC Classification Sufficient	IARC Classification Limited
Coal Tar Distillation	X	
Creosotes		X
Mineral oils, untreated or mildly treated	X	
Shale Oils	X	
Soot (chimney sweeping)	X	

- Pre-modern studies of workers in industries who were likely exposed
  - To mixtures of PAHs,
  - To many other chemical and non-chemical agents
  - To ultraviolet light (outdoor work)
- Of the twelve studies used as evidence by EPA that PAH-containing materials causes skin cancer in humans:
  - 7 are negative studies
  - 5 studies are not relevant to PAH-containing materials or are inconclusive
    - One study is of lumberjacks in Finland
    - One is a historical review of chimney sweeps in England in the 18<sup>th</sup> century

# Skin Cancer

Occupational exposure studies cited by EPA (but not IARC) as evidence of an association between PAH-containing materials and skin cancer.

**Table 3. Summary of human exposure studies cited in EPA (2017), but not in IARC monographs, as providing evidence that PAH-containing materials cause skin cancer.**

Citation	Exposure Group	Study Effect Noted in EPA (2017)	Statistical Significance of Effect Reported in Study
Spinelli et al. (2006)	Aluminum Production	Melanoma	Not significant
Gibbs et al. (2007 a,b)	Aluminum Production	Melanoma	Not significant
Brown & Thornton (1957)	Soot (chimney sweeps)	Scrotal cancer	Not reported & irrelevant
Hammond et al. (1976)	Roofers/water-proofers	Non-melanoma skin cancer	Not significant
Pukkala (1995)	Round-timber workers	Non-melanoma skin cancer	Not relevant <sup>1</sup>
Karlehagen et al. (1992)	Creosote (treatment workers)	Non-melanoma skin cancer	Not relevant <sup>2</sup>
Tornquist et al. (1986)	Creosote (power linesmen)	Non-melanoma skin cancer	Not significant
Roelofzen et al. (2010)	Coal tar (pharmaceutical users)	Non-melanoma skin cancer	Not significant
Pittlekow et al. (1981)	Coal tar (pharmaceutical users)	Non-melanoma skin cancer	Not significant
Maughan et al. (1980)	Coal tar (pharmaceutical users)	Non-melanoma skin cancer	Not significant
Stern et al. (1980)	Patients exposed to carcinogenic psoralens and/or UV light	Non-melanoma skin cancer	Not relevant <sup>3</sup>
Stern et al. (1998)	Patients exposed to coal tar, carcinogenic psoralens, and UV light	Non-melanoma skin cancer	Not relevant <sup>4</sup>

1. "Round-timber workers" work with trees before conversion to lumber and are not exposed to creosote or other wood treatment methods.

2. The study did not control for exposure to sunlight and the authors did not conclude that there was any correlation between creosote exposure and skin cancer.

3. Some patients in this study were exposed to carcinogenic psoralens as well as coal tar and UV light.

4. This study did not include patients exposed to coal tar.

# Lung Cancer

**Table 5. Summary of IARC Lung Cancer Hazard Classifications for Occupations Involving PAH Mixtures**

Mixture or Occupation of Exposure	IARC Classification Sufficient	IARC Classification Limited
Aluminum production	X	
Carbon electrode manufacture		X
Coal gasification	X	
Coal tar pitch (paving and roofing)	X	
Coke production	X	
Diesel exhaust	X	
Indoor emissions from household combustion of biomass fuel (primarily wood) (IARC monograph 95, 2010)		X
Indoor emissions from household combustion of coal (IARC monographs 95 (2010) and 100E (2012a))	X	
Soot (chimney sweeping)	X	

# Basis of current classifications: Lung Cancer

- Studies relied on by IARC provide, **at best, marginal evidence** that lung cancer was increased in workers who were exposed to complex mixtures of chemicals (not just PAHs in PAH-containing substances)
- Twice as many cited studies showed no increased risk of lung cancer than there are positive studies.
  - Of 38 cited studies that were reported to be adequate in quality
    - 25 were negative studies.
    - 13 were positive studies
- Evaluations & classification biased
  - *Positive studies (no matter how weakly positive) given more weight*

# The Scientific Approach: Systematic Review

- Not (yet) adopted by IARC
- EPA claims to be adopting Systematic Review, but no procedures yet issued for public comment

## WHAT IS SYSTEMATIC REVIEW?

- Collect and critically analyze multiple research studies on a topic
- Establish criteria for assessing quality and utility of each study
  - Assess each study for inadequate study design, “risk of bias,” other factors
  - Studies that do not meet the criteria are not included in meta-analysis
- Conduct meta-analyses of data set that passes muster



For PAH-Containing Materials,  
Many Published Systematic  
Reviews of Occupational  
Exposure Studies

# Skin Cancer

- Systematic review conducted by University of British Columbia for Worksafe BC (BC equivalent of OSHA in US)

Found *no* modern epidemiology studies that demonstrate that PAH-containing substances are a cause of human skin cancer in today's world

# STANDARDIZED MORTALITY RATIOS (SMRS) AND POOLED RELATIVE RISKS (RRS) WITH 95 % CONFIDENCE INTERVALS (CIS) FOR LUNG CANCER FOR WORKERS EXPOSED TO POLYCYCLIC AROMATIC HYDROCARBONS IN VARIOUS INDUSTRIES

Industry	No. of Cohorts	Observed/Expected	SMR	Pooled RR (95 % CI)	Reference
Aluminum Production	10	1,314/1,154.7	1.14	1.07 (0.93–1.23)	Rota et al. (2014)
Asphalt Workers	3	827/735.7	1.12	1.59 (0.68–3.76)	Rota et al. (2014)
Carbon Black Production	3	249/201.1	1.24	1.52 (0.91–2.52)	Rota et al. (2014)
Carbon Electrode Manufacturing	6	97/101.6	0.96	1.00 (0.82–1.23)	Bosetti et al. (2007)
Coal Gasification	4	188/87.7	2.14	2.29 (1.98–2.64)	Bosetti et al. (2007)
Coal Tar Distillation	3	65/54.6	1.19	1.21 (0.95–1.55)	Bosetti et al. (2007)
Coke Production	10	762/512.1	1.49	1.58 (1.47–1.69)	Bosetti et al. (2007)
Creosote	2	47/42.4	1.11	1.14 (0.85–1.51)	Bosetti et al. (2007)
Iron and Steel Foundry	13	2,903/2,762.4	1.05	1.31 (1.07–1.61)	Rota et al. (2014)
Roofers	2	138/91.9	1.5	1.51 (1.28–1.78)	Bosetti et al. (2007)

meta-analysis and systematic reviews of Bosetti et al. (2007) and Rota et al. (2014)

**Table 10. Published systematic reviews/meta-analyses of cancer endpoints in occupational exposure studies conducted on cohorts of workers in PAH-involved industries.**

Reference	Industry Group <sup>1</sup>	Lung/ Respiratory tract	Skin	Bladder/ Urinary tract	Larynx	Stomach	Esoph- agus	L&HN <sup>2</sup>	HL <sup>3</sup>	NHL <sup>4</sup>	Leukemia	Multiple Myeloma
Alicandro et al (2016)	PAH-involved							X	X	X	X	X
Armstrong et al (2004)	PAH-involved	X										
Bosetti et al (2007)	PAH-involved	X		X								
Fayerweather (2007)	Roofers and Pavers	X										
Gamble et al (2012)	Diesel exhaust	X										
Mundt et al (2018)	Bitumen (asphalt) workers	X	X	X		X	X					
Paget-Bailey et al (2012)	PAH-involved				X							
Partenan & Boffetta (1994)	Roofers and Pavers	X	X	X		X		X			X	
Rota et al (2014)	PAH-involved	X		X								
Singh et al (2018)	PAH-involved	X										
Spinelli et al (2012)	PAH-involved		X									
Wagner et al (2014)	PAH-involved				X							

<sup>1</sup> “PAH-involved” indicates that multiple industries were considered in the cited meta-analysis.

<sup>2</sup> L&HN: Lymphatic & Hematopoietic Neoplasms

<sup>3</sup> HL: Hodgkin Lymphoma

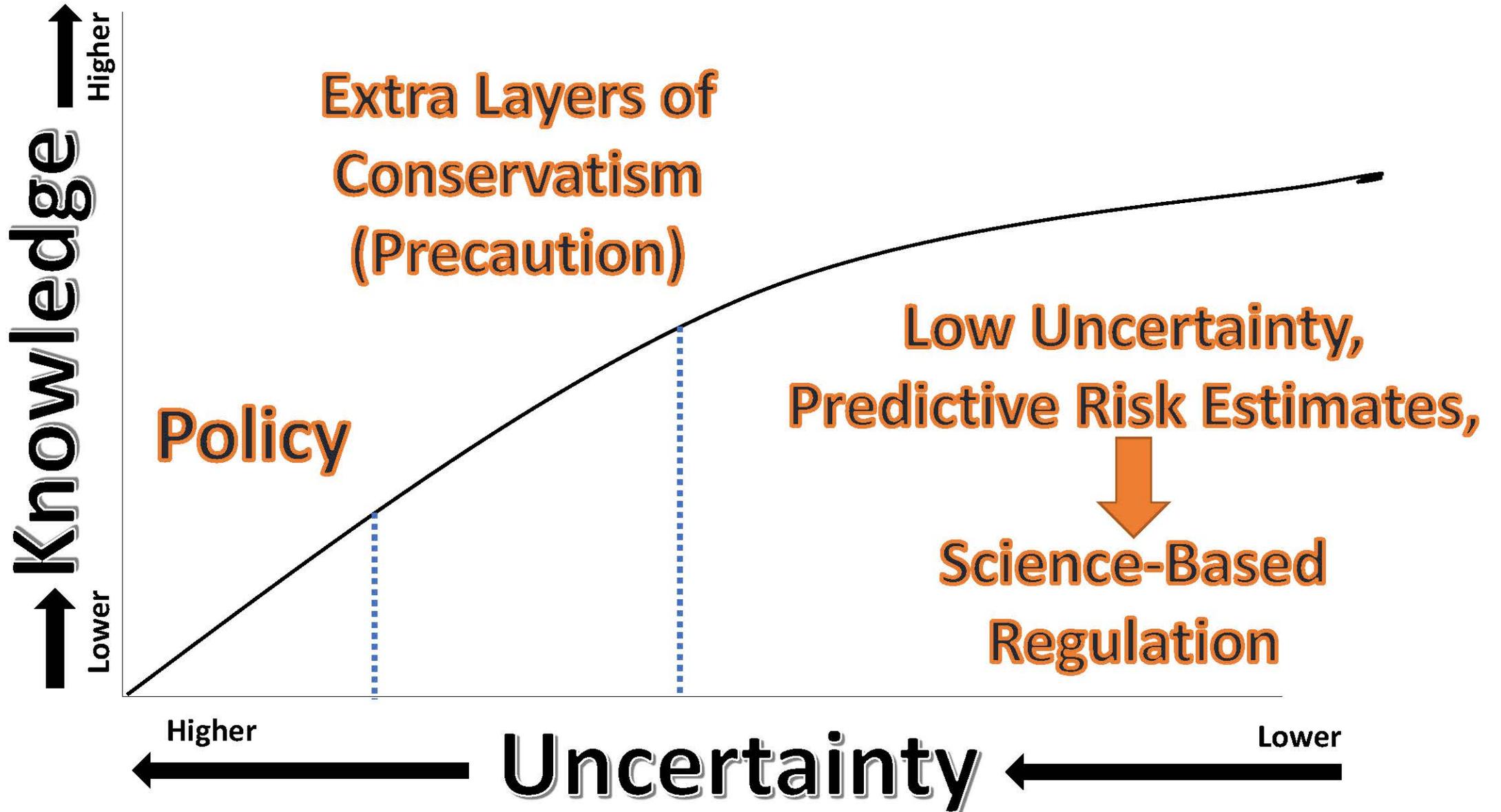
<sup>4</sup> NHL: Non- Hodgkin Lymphoma

# Improved Industrial Hygiene or Improved Study Design?

- Difficult to disentangle
  - Effects related to improved occupational safety procedures
  - Effects related to improved epidemiology study procedures
- Both probably play a role
- “Data” used in existing IARC/EPA hazard assessments were and are inadequate to support claims of “known human carcinogenicity”
  - Should the classification stand just because both PPE and study designs were inadequate decades ago?

# Some impacts of out-of-date hazard assessments

- Misinformation informs regulation
- Misinformation impacts litigation (cf. glyphosate)
- Compliance costs that may not be warranted
- Missed opportunities because of unwarranted risk aversion
- Misdirected attention of the public
- Alarmism
- Proliferation of uninformed science
- Impedes progress towards evidence-based regulation
- Warps markets



# Recommendations

- Trade associations & companies make adoption of Systematic Review by government review bodies a priority in Government Affairs activities
- Trade associations & companies prioritize adoption of quantitative methods in hazard classification reviews
  - E.g. What is meant by “strong evidence?”
- Is the current practice of basing hazard classification on the concept that an effect could be seen under certain circumstances helping understanding of risk?
- PAH-involved industries prioritize requests that IARC (global) and EPA (US) conduct comprehensive Systematic Reviews of hazard classifications of their industries



Questions?  
Discussion?