(Environmental and) Occupational Health Perspective on Evaluating Chemical Mixtures

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The views expressed are those of the author and do not necessarily express the views of the National Institute for Occupational Safety and Health

One Scientist's Journey from a Regulatory…

CHEMICAL

…to a Non-Regulatory…

MIXTURES

…Federal Government Agency

(And his search for scientists who believe there is room for those who want to focus on "simple" mixtures)

Respiratory Health Division
National Institute for Occupational Safety and Health (NIOSH)
Morgantown, WV

Morgantown in Autumn

Occupational Safety and Health in the U.S.

Regulation / Enforcement

Department of Labor
(DOL)

Mine Safety and Health Administration
(MSHA)

Occupational Safety and Health Administration
(OSHA)

Research / Recommendations

Department of Health and Human Services
(DHHS)

Centers for Disease Control and Prevention
(CDC)

National Institute for Occupational Safety and Health
(NIOSH)

My Life Prior to Joining NIOSH…

(Personal) Experience with Multipollutant Science Assessments at the U.S. EPA

- **Multipollutant vs. Mixture?**
- **Multipollutant:** Thought by some to suggest a discrete number of chemicals or pollutants
- **Mixtures:** Terminology preferred by scientists; policy makers express concerns over the inclusion of an unmanageable set of chemicals
- Both are used and both are correct
- Real world: Populations of interest exposed to very complex mixtures

National Ambient Air Quality Standards (NAAQS) Background

- Ambient standards for pollutants considered to be harmful to public health and the environment
  - Indicator
  - Averaging Time
  - Level
  - Form
- Clean Air Act (CAA) requires EPA to review “air quality criteria” and NAAQS every 5 years for “criteria” pollutants (ozone, PM, CO, SO_2, NO_2, lead) (CAA §§108 and 109)
  - Air quality criteria are to “accurately reflect latest scientific knowledge”
  - Primary (health-based) and secondary (welfare-based) NAAQS based on the air quality criteria

National Ambient Air Quality Standards (NAAQS)

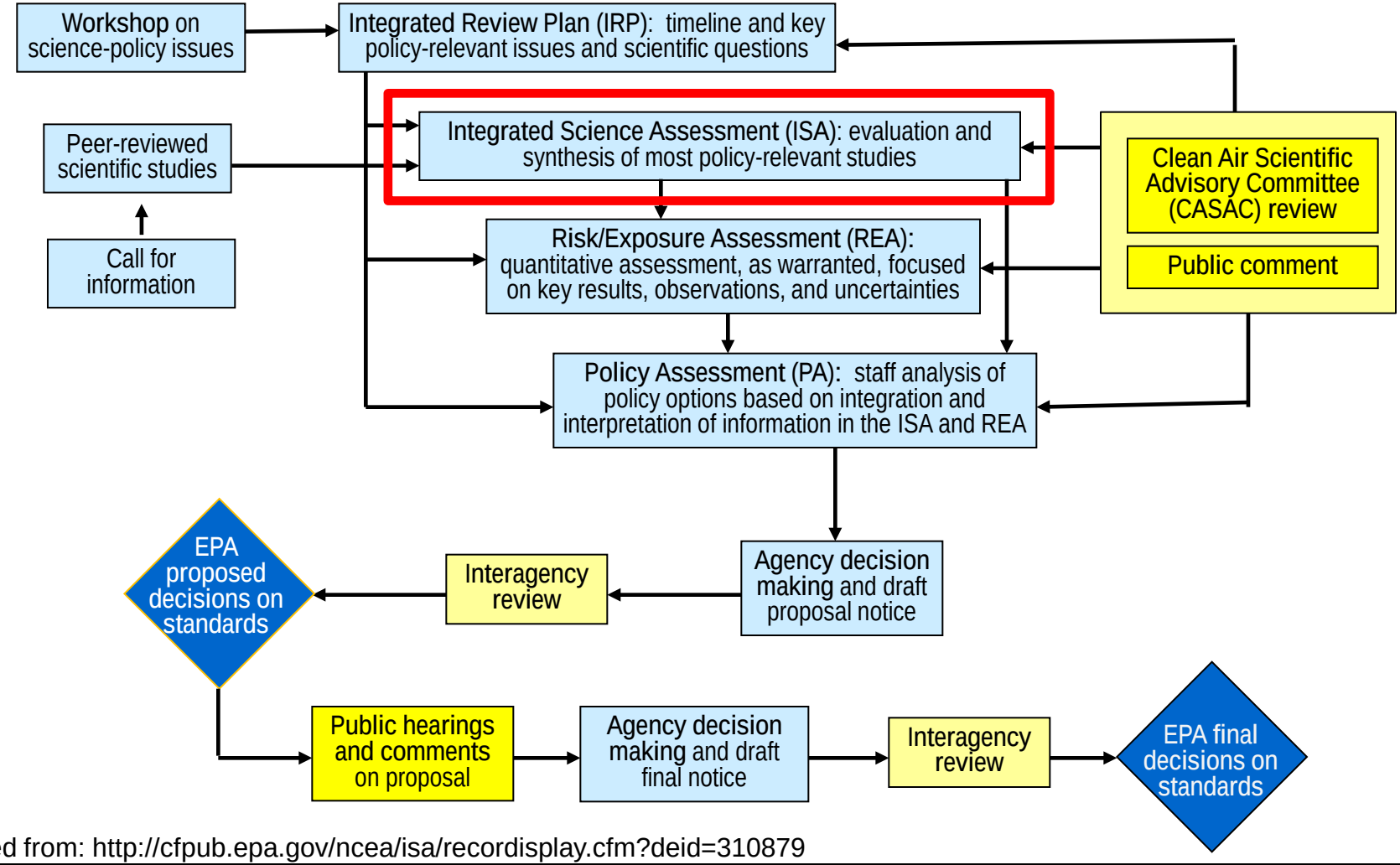
The Clean Air Act, which was last amended in 1990, requires EPA to set National Ambient Air Quality Standards (40 CFR part 50) for pollutants considered harmful to public health and the environment. The Clean Air Act identifies two types of national ambient air quality standards. ***Primary standards*** provide public health protection, including protecting the health of "sensitive" populations such as asthmatics, children, and the elderly. ***Secondary standards*** provide public welfare protection, including protection against decreased visibility and damage to animals, crops, vegetation, and buildings.

The EPA has set National Ambient Air Quality Standards for six principal pollutants, which are called "criteria" pollutants. Periodically, the standards are reviewed and may be revised. The current standards are listed below. Units of measure for the standards are parts per million (ppm) by volume, parts per billion (ppb) by volume, and micrograms per cubic meter of air ($\mu g/m^3$).

Pollutant [links to historical tables of NAAQS reviews]		Primary/ Secondary	Averaging Time	Level	Form
Carbon Monoxide (CO)		primary	8 hours	9 ppm	Not to be exceeded more than once per year
			1 hour	35 ppm	
Lead (Pb)		primary and secondary	Rolling 3 month period	0.15 $\mu g/m^3$ (1)	Not to be exceeded
Nitrogen Dioxide (NO_2)		primary	1 hour	100 ppb	98th percentile of 1-hour daily maximum concentrations, averaged over 3 years
		primary and secondary	1 year	53 ppb (2)	Annual Mean
Ozone (O_3)		primary and secondary	8 hours	0.070 ppm (3)	Annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years
Particle Pollution (PM)	$PM_{2.5}$	primary	1 year	12.0 $\mu g/m^3$	annual mean, averaged over 3 years
		secondary	1 year	15.0 $\mu g/m^3$	annual mean, averaged over 3 years
		primary and secondary	24 hours	35 $\mu g/m^3$	98th percentile, averaged over 3 years
	PM_{10}	primary and secondary	24 hours	150 $\mu g/m^3$	Not to be exceeded more than once per year on average over 3 years
Sulfur Dioxide (SO_2)		primary	1 hour	75 ppb (4)	99th percentile of 1-hour daily maximum concentrations, averaged over 3 years
		secondary	3 hours	0.5 ppm	Not to be exceeded more than once per year

http://www3.epa.gov/ttn/naaqs/criteria.html

National Ambient Air Quality Standards (NAAQS) Review Process



Adapted from: http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879

Mixtures in the ISAs

- 2004 NRC report - *Air Quality Management in the United States* - Recommendation: Address multiple pollutants in the NAAQS review and standard setting process
  - "Although the committee does not believe that the science has evolved to a sufficient extent to permit the development of multipollutant NAAQS, it would be scientifically prudent to begin to review and develop NAAQS for related pollutants in parallel and simultaneously"

- Considerations of mixtures of air pollutants
  - "The criteria…shall include information on…the types of air pollutants which, when present in the atmosphere may interact with such pollutant to produce an adverse effect…" (CAA § 108)
  - Mixtures currently considered to the extent practicable within the ISAs to inform effects of a given pollutant (focus on single pollutant)

2011 EPA Multipollutant Workshop

- Purpose:
  "…discuss [the] challenges, along with opportunities and future research needs related to multipollutant approaches for the evaluation of health risks associated with exposures to air pollution."

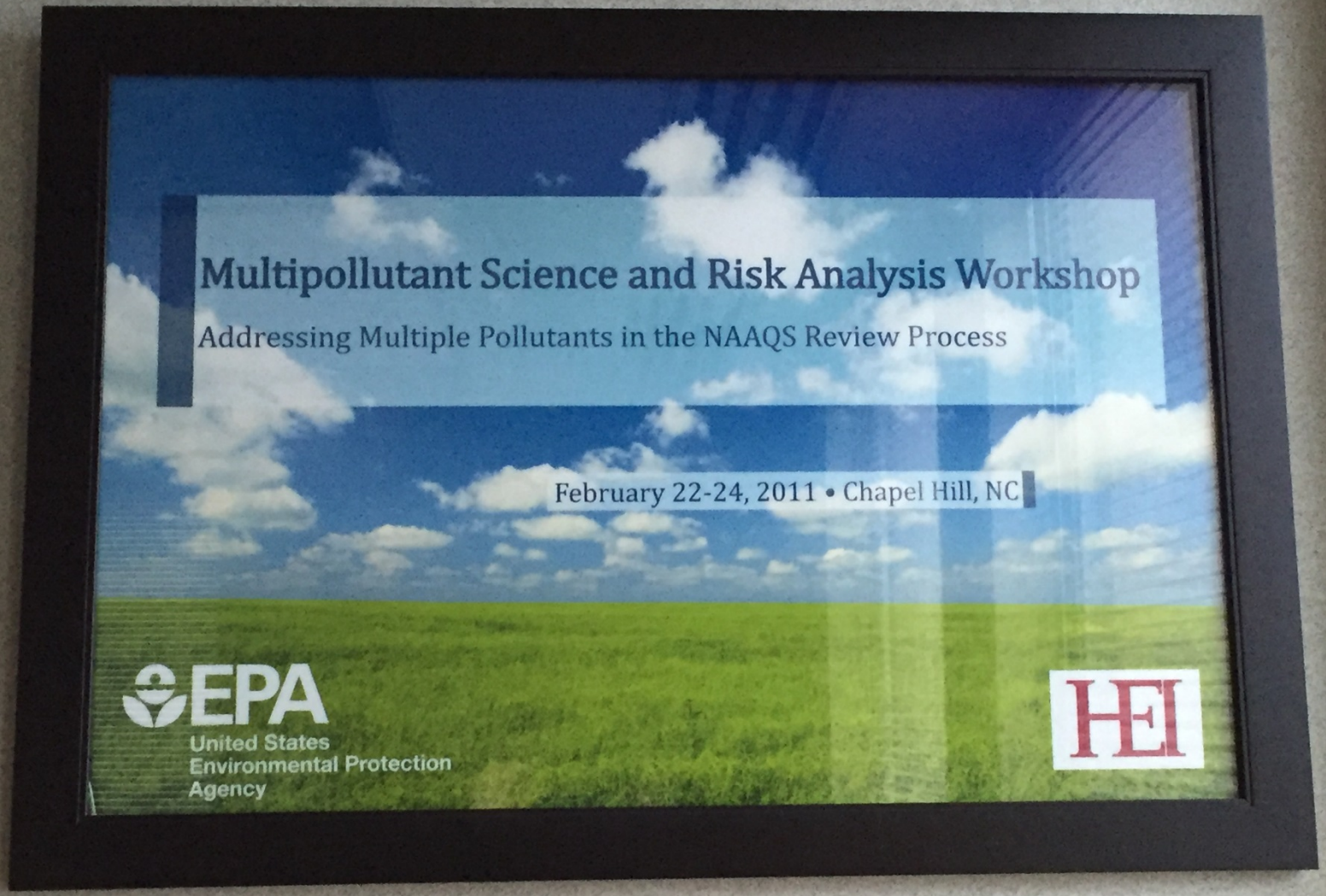
- Attendees and panelists from Government, Academia, Industry and Environmental Advocacy Groups

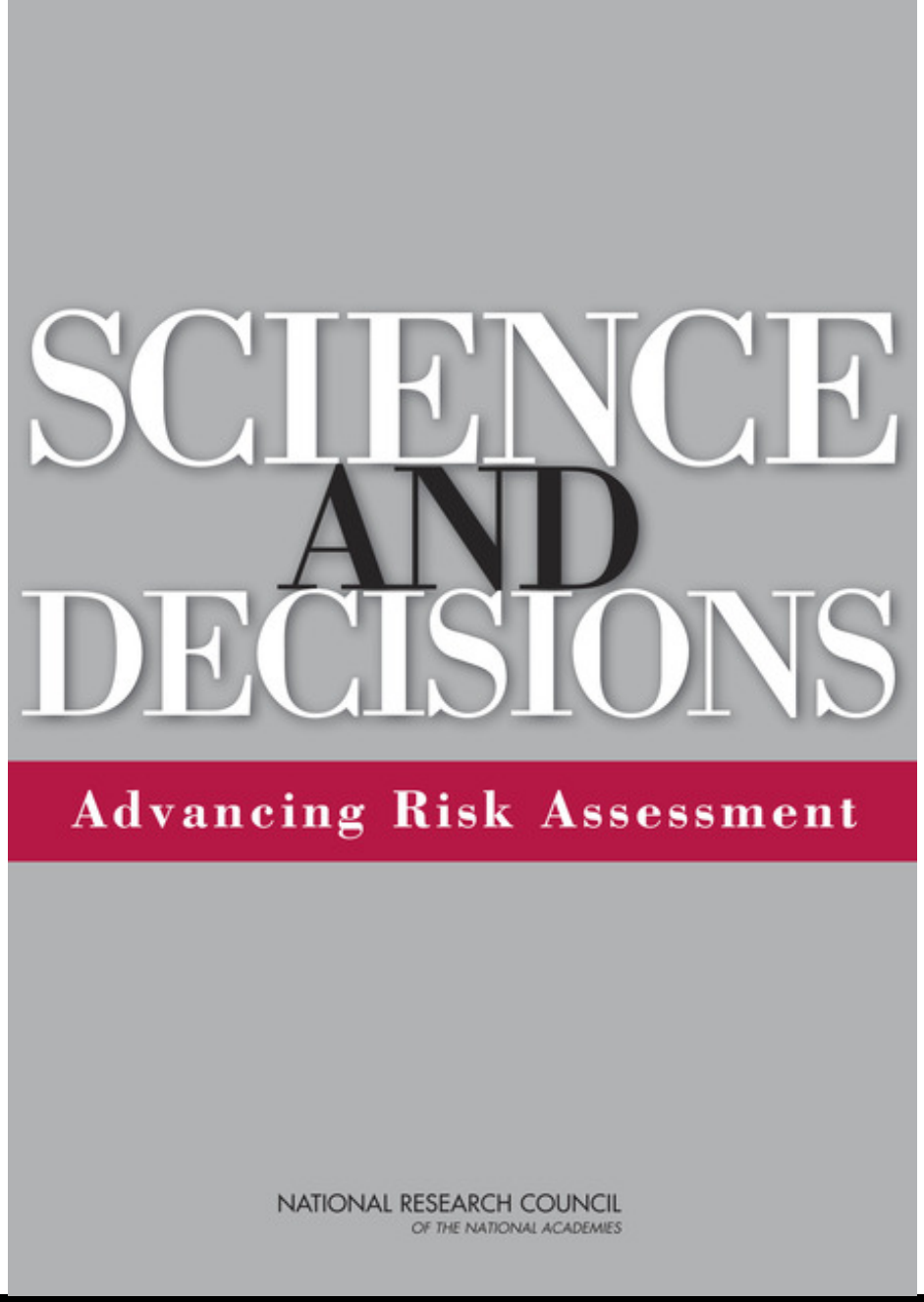
- No discussion of potential development of multipollutant NAAQS

Multipollutant Assessments: Widespread Support

- Mauderly et al. (2010), “Is the air pollution health research community prepared to support a multipollutant air quality management framework?”
  - “…increasingly explicit emphasis on multipollutant issues can be expected to parallel regulatory agency commitment to multipollutant air quality management.”
- Greenbaum and Shaikh (2010), “First steps toward multipollutant science for air quality decisions”
  - “Taking these actions will not be easy, but given that populations are never exposed to one pollutant at a time, and that efforts to control pollutants at lower and lower levels have become increasingly contentious as well as difficult, getting the science ‘right’ on reducing exposure to the mixture seems to be the only reasonable way forward.”
- Johns et al. (2012), “Practical advancement of multipollutant scientific and risk assessment approaches for ambient air pollution”
  - “…increasing the emphasis on multipollutant approaches may allow for a better understanding of the types of air pollutant mixtures most likely to result in adverse health effects, which could, in turn, facilitate the identification of control strategies to minimize exposures to these mixtures.”

Current Status?


Multipollutant Science and Risk Analysis Workshop
Addressing Multiple Pollutants in the NAAQS Review Process
February 22-24, 2011 • Chapel Hill, NC
EPA
United States
Environmental Protection
Agency
HEI



- Committee on Improving Risk Analysis Approaches used by the U.S. Environmental Protection Agency (2009)
- Recommendations for Improving Risk Analysis Approaches
- Chapter 7: Implementing Cumulative Risk Assessment
- Consider chemical and nonchemical stressors

Occupational Exposures?

NIOSH Project: "Integration of Cumulative Risk Assessment into Occupational Safety and Health"

- Provide occupational health professionals with suite of innovative tools, resources and materials
  - Conceptual occupational framework for conducting cumulative risk assessments to protect workers
  - Development of practical tools to assist occupational health professionals in refining risk management and risk communications efforts
  - Including both chemical and non-chemical stressors
- Highlight the need to consider occupational risk factors in conducting human health risk assessments to protect public health
- External partners from academia, private sector, and other Government Agencies
- Potentially high impact effort that may form the foundation for additional mixtures research

Coal Workers' Health Surveillance Program

Established to:

- *Detect coal workers' pneumoconiosis (CWP) and prevent its progression in individual miners*
- *Provide information for evaluation of temporal and geographic trends in CWP*

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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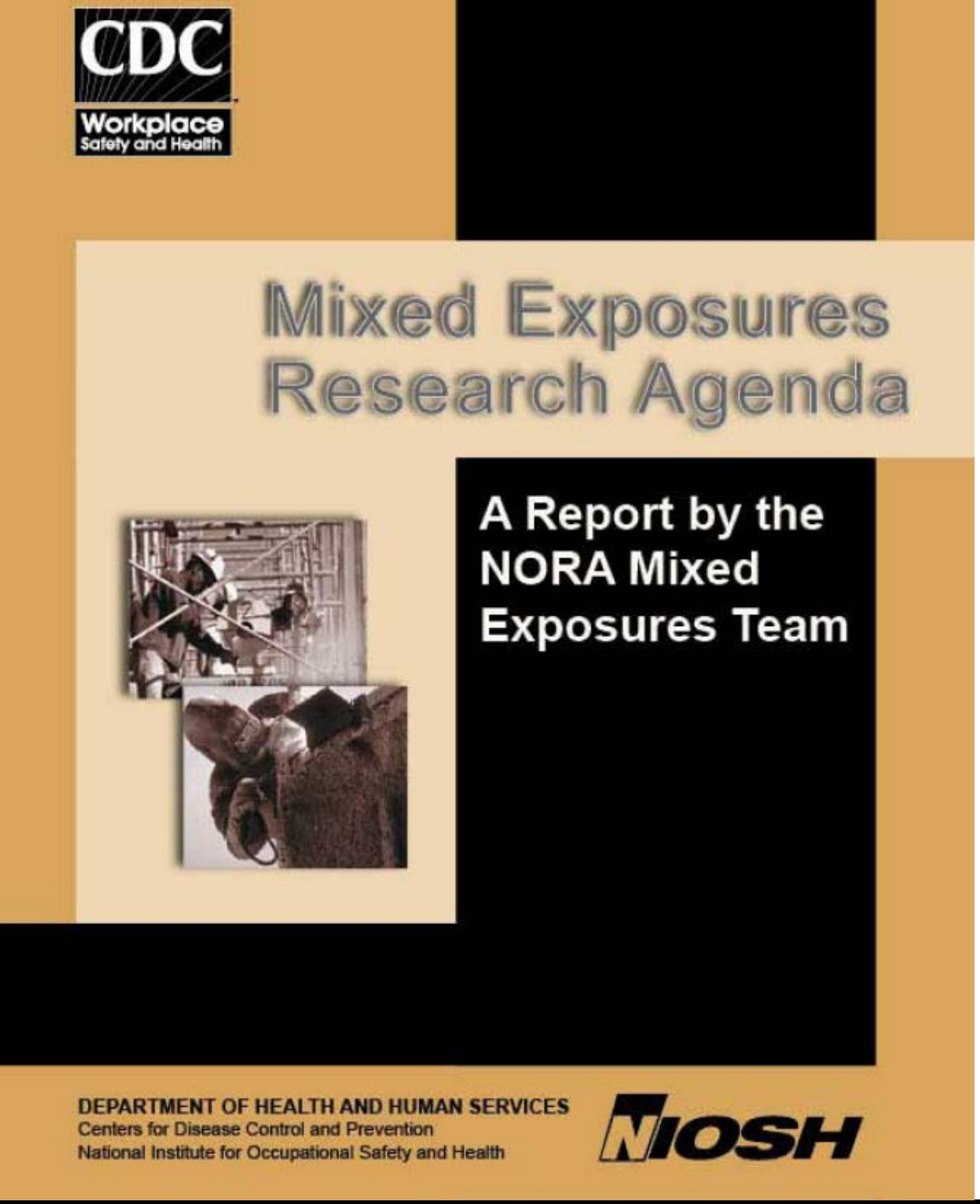
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

Coal Dust

- Coal dust as a complex mixture containing more than 50 different elements and their oxides
- MSHA Rule to lower miners' exposure to respirable coal mine dust
  - Final rule signed May 1, 2014
  - Lowers standard from 2.0 mg/m^3 to 1.5 mg/m^3
  - Based in part on recommendations from NIOSH (1995)
- Expansion of Coal Workers' Health Surveillance Program
  - Include miners working in both underground and surface mines
  - Expands medical surveillance to include spirometry and symptom assessment in addition to chest radiography
- Increase in prevalence of coal workers' pneumoconiosis
  - Attempting to find the "silver bullet" in the coal mine dust?
  - Silica and coal components are both important contributors to pneumoconiosis (dust-induced lung disease) in coal miners



Research Priorities (2004)

- Surveillance methods to identify the number of workers exposed to “mixtures of concern”
- Conduct research to better understand the toxicology and biological mechanisms of mixed exposures
- Develop methods that can be used to measure and predict deviations from additivity
- Identify, validate and characterize the health outcome for biomarkers of exposure and response for workers exposed to mixtures
- **Not plausible to address full universe of possible mixed exposures; Scope of research targets must be somewhat limited**

EXPOSOME?

Workplace Safety & Health Topics

EXPOSOME AND EXPOSOMICS

Overview

What is the exposome?

Success in mapping the human genome has fostered the complementary concept of the "exposome". The exposome can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health. An individual's exposure begins before birth and includes insults from environmental and occupational sources. Understanding how exposures from our environment, diet, lifestyle, etc. interact with our own unique characteristics such as genetics, physiology, and epigenetics impact our health is how the exposome will be articulated.

Exposomics is the study of the exposome and relies on the application of internal and external exposure assessment methods. Internal exposure relies on fields of study such as genomics, metabonomics, lipidomics, transcriptomics and proteomics. Commonalities of these fields include 1) use of biomarkers to determine exposure, effect of exposure, disease progression, and susceptibility factors, 2) use of technologies that result in large amounts of data and 3) use of data mining techniques to find statistical associations between exposures, effect of exposures, and other factors such as genetics with disease. External exposure assessment relies on measuring environmental stressors. Common approaches include using direct reading instruments, laboratory-based analysis, and survey instruments. The extent to which internal and external exposure assessment will contribute to our understanding of the exposome is being

Contact Us:

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Centers for Disease Control and Prevention
800-CDC-INFO
(800-232-4636)
TTY:
(888) 232-6348

New Hours of Operation
8am-8pm ET/Monday-Friday
Closed Holidays

Contact CDC-INFO

Additive Mixture Formulae

- Primarily for noncancer endpoints
- ACGIH
  - "When two or more hazardous substances have a similar toxicological effect on the same target organ or system, their combined effect, rather than that of either individually, should be given primary consideration"

$$\frac{C_1}{T_1} + \frac{C_2}{T_2} + \ \dots \frac{C_n}{T_n}$$

  - Where sum exceeds unity, threshold limit should be considered as being exceeded
  - Assumption of additivity
  - Exceptions when there is "good reason to believe" that effects are not additive, e.g., antagonistic or synergistic

- Human Health Risk Assessment (EPA and ATSDR)
  - Hazard Quotients and Indices

$$HI = \frac{EC_1}{RfC_1} + \frac{EC_2}{RfC_2} + \ \dots \frac{EC_n}{RfC_n}$$

  - Hazard Index > 1 indicates some increased risk

Considerations of Mixtures: OSHA

- 29 CFR 1910.1000(d)(2)(i)
- Mixture of air contaminants
  - $E_m = (C_1 \div L_1 + C_2 \div L_2) + \ldots (C_n \div L_n)$

    Where:

    E_m is the equivalent concentration for the mixture

    C is the concentration of a particular contaminant

    L is the exposure limit for that substance
  - The value of E_m shall not exceed unity

- Citable?
- Search of violations per standard: 1910.1000(d)(2)(i) cited 6 times in last 10 years

Additive Mixture Formula in NIOSH?

The New England Journal of Medicine

CLINICAL BRONCHIOLITIS OBLITERANS IN WORKERS AT A MICROWAVE-POPCORN PLANT

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ABSTRACT

Background In May 2000, eight persons who had formerly worked at a microwave-popcorn production plant were reported to have severe bronchiolitis obliterans. No recognized cause was identified in the plant. Therefore, we medically evaluated current employees and assessed their occupational exposures.

Methods Questionnaire responses and spirometric findings in participating workers were compared with data from the third National Health and Nutrition Examination Survey, after adjustment for age and smoking status. We evaluated the relation between exposures and health-related outcomes by analyzing the rates of symptoms and abnormalities according to current and cumulative exposure to diacetyl, the predominant ketone in artificial butter flavoring and in the air at the plant.

Results Of the 135 current workers at the plant, 117 (87 percent) completed the questionnaire. These 117 workers had 2.6 times the expected rates of chronic cough and shortness of breath, according to comparisons with the national data, and twice the expected rates of physician-diagnosed asthma and chronic bronchitis. Overall, the workers had 3.3 times the expected rate of airway obstruction; those who had never smoked had 10.8 times the expected rate. Workers directly involved in the production of microwave popcorn had higher rates of shortness of breath on exertion and skin problems that had developed since they started work than workers in other parts of the plant. There was a strong relation between the quartile of estimated cumulative exposure to diacetyl and the frequency and extent of airway obstruction.

Conclusions The excess rates of lung disease and lung-function abnormalities and the relation between exposure and outcomes in this working population indicate that they probably had occupational bronchiolitis obliterans caused by the inhalation of volatile butter-flavoring ingredients. (N Engl J Med 2002; 347:330-8.)

IN May 2000, eight persons who had formerly worked at a plant that produces microwave popcorn were reported to the Missouri Department of Health to have bronchiolitis obliterans.[1,2] These workers had become ill during the period from 1993 to 2000, while employed at the popcorn plant, and none had reported an incident of presumed overexposure that preceded their symptoms. Four had worked in the room where microwave-popcorn flavoring agents were mixed, and four had worked only in the microwave-popcorn packaging areas. On the basis of these cases, we conducted medical examinations and environmental surveys of workers employed at the plant in November 2000 to determine whether any of them had signs or symptoms of this illness and whether exposures at the plant contributed to the disease.

The production area of the microwave-popcorn plant encompassed a flavor-mixing room, a quality-control room for popping sample product, a maintenance shop, and packaging lines where microwavable bags were filled with popcorn and flavorings, packaged, and boxed. The ingredients of the flavorings included soybean oil, salt, butter flavoring, and coloring agents. In the mixing room, one worker per shift opened the lid of an oil tank that was heated to approximately 130°F (54°C) and added flavorings in batch operations. The flavoring mixture was then pumped into heated holding tanks above the microwave-popcorn packaging lines. On the packaging lines, the kernel popcorn and flavoring mixture were added to the microwavable bags by a machine operator; the bags were then sealed, labeled, and boxed; and the boxes were stacked on pallets. The following areas of the plant were physically separate from the microwave-popcorn production area: the warehouse, the bag-printing area, outdoors, the line where unflavored kernel popcorn was packaged (in polyethylene bags), and the offices where management and clerical activities were performed.

Analysis of air samples from the mixing room identified more than 100 volatile organic compounds. There were no known occupational causes[3] of bron-

From the Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, W.Va. (K.K., A.G., G.K., K.F., P.L.E.); and the Office of Epidemiology, Missouri Department of Health and Senior Services, Jefferson City (E.J.S.). Address reprint requests to Dr. Kreiss at NIOSH, H2800, 1095 Willowdale Rd., Morgantown, WV 26505, or at kkreiss@cdc.gov.

Flavoring-Related Lung Disease

- Diacetyl exposure in microwave popcorn plants (butter flavoring)
- 8 sentinel cases of obliterative bronchiolitis (May 2000)
  - Rare inflammatory disease of small airways
  - 4 on lung transplant lists
- 2,3-Pentanedione as a substitute
  - Very similar chemical structure
  - Similar pathological responses observed in toxicological studies
- New exposures of concern
  - Coffee flavoring and roasting
  - Both alpha-diketones measured
- Development of NIOSH Criteria Document and proposed REL

29 USC 669(a)(3)

The Secretary of Health and Human Services, on the basis of such research, demonstrations, and experiments, and any other information available to him, shall develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels that are safe for various periods of employment, including but not limited to the exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience.

29 USC 671(c)(1)

The [National Institute for Occupational Safety and Health] is authorized to - (1) develop and establish recommended occupational safety and health standards

Other Specific Examples of Current Mixtures Work Within NIOSH

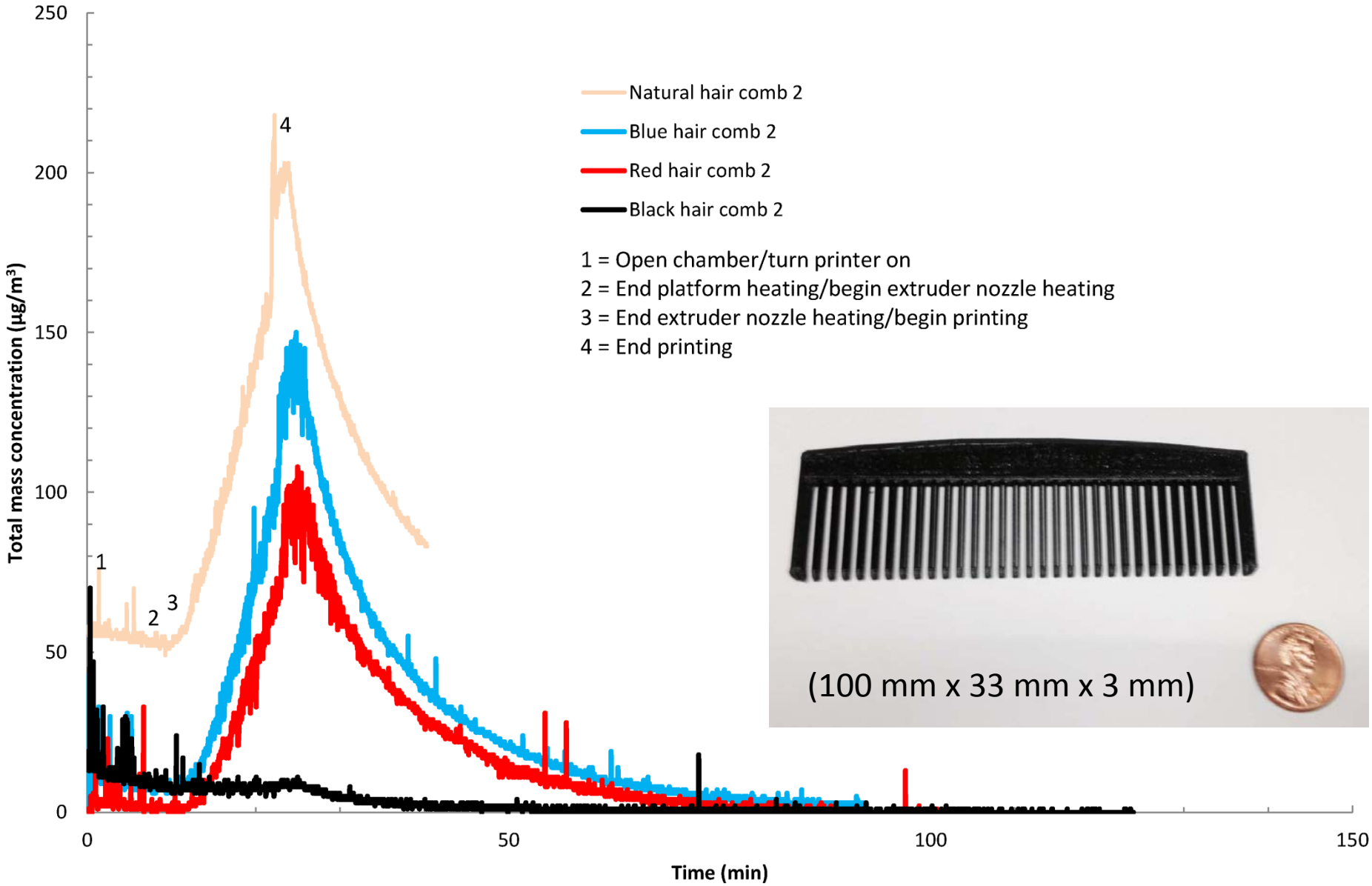
NIOSH Laboratory Studies

- Toxicological Effects of Silica and Diesel Exhaust
  - Gas extraction workers exposed to crystalline silica and diesel exhaust
  - Using in-vivo and in-vitro models, establish dose-response relationships for inhaled silica, and diesel exhaust, alone and in combination
  - Evaluating toxicity in the lungs and extra-pulmonary organ systems
- Health Effects of Inhaled Crude Oil Vapors
  - Many workers employed in the oil and gas industry
  - Crude oil is a complex mixture of hydrocarbons, other chemicals, and metals
    - Toxicities of many of the components of crude oil are well characterized
    - Difficult to predict health effect of mixtures based on effects of those individual components
  - Animals exposed to crude oil vapor in an inhalation chamber at various concentrations
  - Evaluate effects on respiratory, cardiovascular and central nervous systems

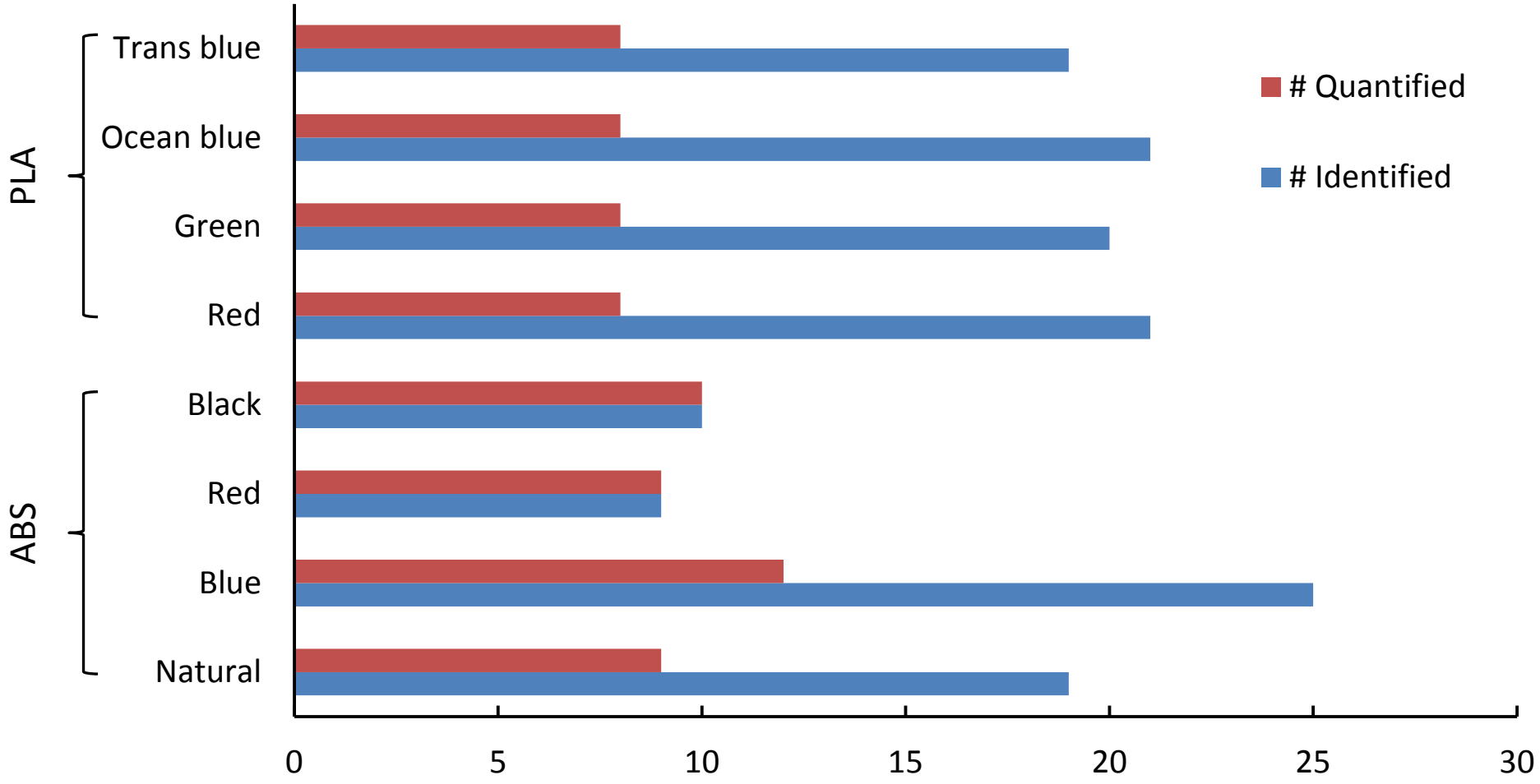
Laboratory Study: 3-D Printing

3-D Printing

Preliminary Results – Filament Color



VOC Mixtures Emitted by 3-D Printers



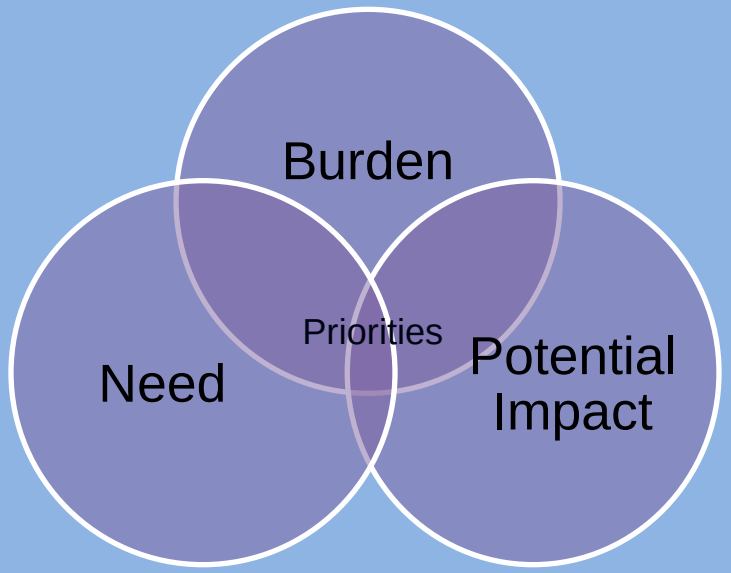
NIOSH Field Study

- Acute Effects of Exposures to Cleaning and Disinfecting Chemicals
  - Epidemiologic evidence of increased risk of asthma in occupations that perform cleaning or disinfecting tasks
  - Healthcare workers
- Peak Exposures
  - Intermittent high level exposures have the potential to contribute to acute effect
  - Peak exposures not consistently defined or measured
- Mixed Exposures
  - Most cleaning products are complex mixtures
    - Irritants (e.g., chlorinated compounds)
    - Sensitizers (e.g., quaternary ammonium compounds)
  - Principal component analysis of multiple exposures

Assessing and Aligning NIOSH Research Priorities

Underlying Premises

- NIOSH should be doing the most important work to protect the nation's workforce
- NIOSH priorities should be fundamentally based on **burden, need, and potential impact**



Burden

- Morbidity, mortality, and injury
- Risk (hazard plus exposure)
- Size of population at risk
- Economic impact
- Quality of life

Need

- The most efficient effort to address burden
- Based on ”gap determination” – what is needed?
- Comparative advantage
- Stakeholder input

Potential Impact

- Assessing the likelihood that investment will fill an identified need
- Forward looking – likely impact
- Used to compare options

Achieved Impact

- Retrospective – did investments make a difference?
- “Impact Science” – scientific approaches to assess impact

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- Dr. Abbas Virji

Comments?

Questions?

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