(Environmental and) Occupational Health Perspective on Evaluating Chemical Mixtures

EOH Technical Symposium
California State University, Northridge
March 2, 2016

Doug Johns, Ph.D.
Deputy Director, Respiratory Health Division
CDC/NIOSH
djohns@cdc.gov
(304) 285-6384
DISCLAIMER

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)
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; policymakers 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 (µg/m³).

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Primary/Secondary</th>
<th>Averaging Time</th>
<th>Level</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon Monoxide (CO)</td>
<td>primary</td>
<td>8 hours</td>
<td>9 ppm</td>
<td>Not to be exceeded more than once per year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 hour</td>
<td>35 ppm</td>
<td></td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>primary and secondary</td>
<td>Rolling 3 month period</td>
<td>0.15 µg/m³ (^{(1)})</td>
<td>Not to be exceeded</td>
</tr>
<tr>
<td>Nitrogen Dioxide (NO₂)</td>
<td>primary</td>
<td>1 hour</td>
<td>100 ppb</td>
<td>98th percentile of 1-hour daily maximum concentrations, averaged over 3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 year</td>
<td>55 ppb (^{(2)})</td>
<td>Annual Mean</td>
</tr>
<tr>
<td>Ozone (O₃)</td>
<td>primary and secondary</td>
<td>8 hours</td>
<td>0.070 ppm (^{(3)})</td>
<td>Annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years</td>
</tr>
<tr>
<td>Particle Pollution (PM)</td>
<td>PM₂.₅</td>
<td>primary</td>
<td>1 year</td>
<td>12.0 µg/m³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>secondary</td>
<td>1 year</td>
<td>15.0 µg/m³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>primary and secondary</td>
<td>24 hours</td>
<td>35 µg/m³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>primary and secondary</td>
<td>24 hours</td>
<td>150 µg/m³</td>
</tr>
<tr>
<td>Sulfur Dioxide (SO₂)</td>
<td>primary</td>
<td>1 hour</td>
<td>75 ppb (^{(4)})</td>
<td>98th percentile of 1-hour daily maximum concentrations, averaged over 3 years</td>
</tr>
<tr>
<td></td>
<td>secondary</td>
<td>3 hours</td>
<td>0.5 ppm</td>
<td>Not to be exceeded more than once per year</td>
</tr>
</tbody>
</table>
**National Ambient Air Quality Standards (NAAQS) Review Process**

- **Workshop on science-policy issues**
- **Integrated Review Plan (IRP):** timeline and key policy-relevant issues and scientific questions
  - **Integrated Science Assessment (ISA):** evaluation and synthesis of most policy-relevant studies
  - **Risk/Exposure Assessment (REA):** quantitative assessment, as warranted, focused on key results, observations, and uncertainties
- **Clean Air Scientific Advisory Committee (CASAC) review**
- **Public comment**
- **Policy Assessment (PA):** staff analysis of policy options based on integration and interpretation of information in the ISA and REA
- **EPA proposed decisions on standards**
- **Interagency review**
- **Agency decision making and draft proposal notice**
- **Public hearings and comments on proposal**
- **Agency decision making and draft final notice**
- **Interagency review**
- **EPA final decisions on standards**

Adapted from: [http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879](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
• 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
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/m³ to 1.5 mg/m³
  – 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

- 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?
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, metabolomics, 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
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”

\[
\frac{C_1}{T_1} + \frac{C_2}{T_2} + \ldots + \frac{C_n}{T_n}
\]

- 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

\[
HI = \frac{EC_1}{RfC_1} + \frac{EC_2}{RfC_2} + \ldots + \frac{EC_n}{RfC_n}
\]

- Hazard Index > 1 indicates some increased risk
Considerations of Mixtures: OSHA

- 29 CFR 1910.1000(d)(2)(i)
- Mixture of air contaminants
  - $E_m = \left( \frac{C_1}{L_1} + \frac{C_2}{L_2} \right) + \ldots + \left( \frac{C_n}{L_n} \right)$
  
  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?
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
CRITERIA FOR A RECOMMENDED STANDARD

Occupational Exposure to Diacetyl and 2,3-Pentanedione

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

- Natural hair comb 2
- Blue hair comb 2
- Red hair comb 2
- Black hair comb 2

1 = Open chamber/turn printer on
2 = End platform heating/begin extruder nozzle heating
3 = End extruder nozzle heating/begin printing
4 = End printing

(100 mm x 33 mm x 3 mm)
VOC Mixtures Emitted by 3-D Printers

PLA
- Trans blue
- Ocean blue
- Green
- Red

ABS
- Black
- Red
- Blue
- Natural

# Quantified
# Identified
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
Acknowledgments

Special Thanks To:
• CSUN EOH Symposium Organizing Committee
• Salvina Restivo
• Bridget Sullivan
• Dr. Michael Sullivan

NIOSH Scientific Staff:
• Dr. Scott Dotson
• Dr. Paul Siegel
• Dr. Aleks Stefaniak
• Dr. Abbas Virji
Comments?
Questions?

Doug Johns, Ph.D.
Deputy Director, Respiratory Health Division
CDC/NIOSH
djohns@cdc.gov
(304) 285-6384