CUMULATIVE RISK ASSESSMENT:
INTEGRATION OF THE OCCUPATIONAL ENVIRONMENT

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- The findings and conclusions in this presentation have not been formally disseminated by the National Institute for Occupational Safety and Health (NIOSH) and should not be construed to represent any agency determination or policy.

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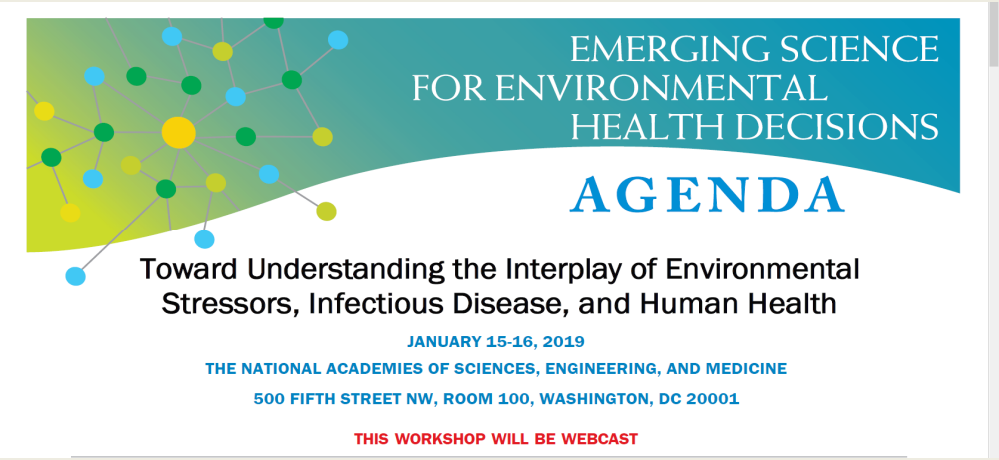
VINYL CHLORIDE MONOMER EXPOSURE AND HEPATITIS B INFECTION

- Wong et al. [2003] investigated the potential interaction of vinyl chloride monomer (VCM) exposure and Hepatitis B infection (HBsAg)- outcome measure- liver cancer
- Case control study of 4096 male workers from 6 polyvinyl chloride polymerization plants in Taiwan
  - 18 patients with liver cancer / 68 control subjects matched for age and specific plant employment were selected
  - *HBsAg- Negative* subjects with low exposures (no tank cleaning) were used as reference population
- Results
  - *HBsAg-Negative* with high exposure- 4.0-fold greater risk of liver cancer (95% CI=0.2-69.1)
  - *HBsAg- Positive* with low exposure- 25.7-fold greater risk of liver cancer (95% CI= 2.9-229.4)
  - *HBsAG-Positive* with high exposure- 396- fold greater risk of liver cancer (95% CI= 22.6-∞)

VINYL CHLORIDE MONOMER EXPOSURE AND HEPATITIS B INFECTION

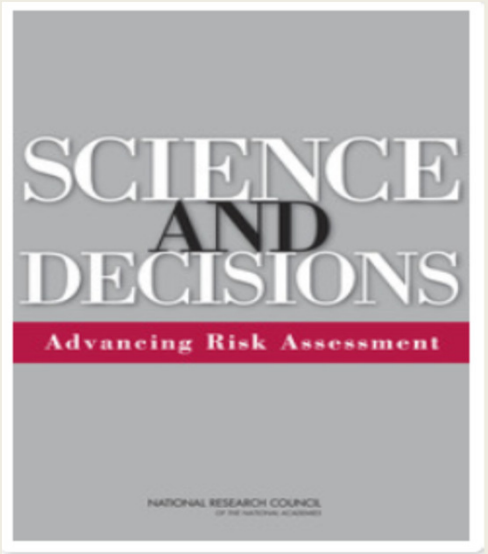
- Conclusions- Potential Interaction between *HPsAG- Positive* status and high VCM exposure on liver cancer
- Limitation:
  - Small number of subjects (with liver cancer)
  - Hepatocellular carcinoma/angiosarcoma not specifically diagnosed



CUMULATIVE RISK

National Academies of Science Definition

- *"The **combination of risks** posed by aggregate **exposure to multiple agents or stressors** in which aggregate exposure is exposure **by all routes and pathways and from all sources** of each given agent or stressor."*



NRC 2009

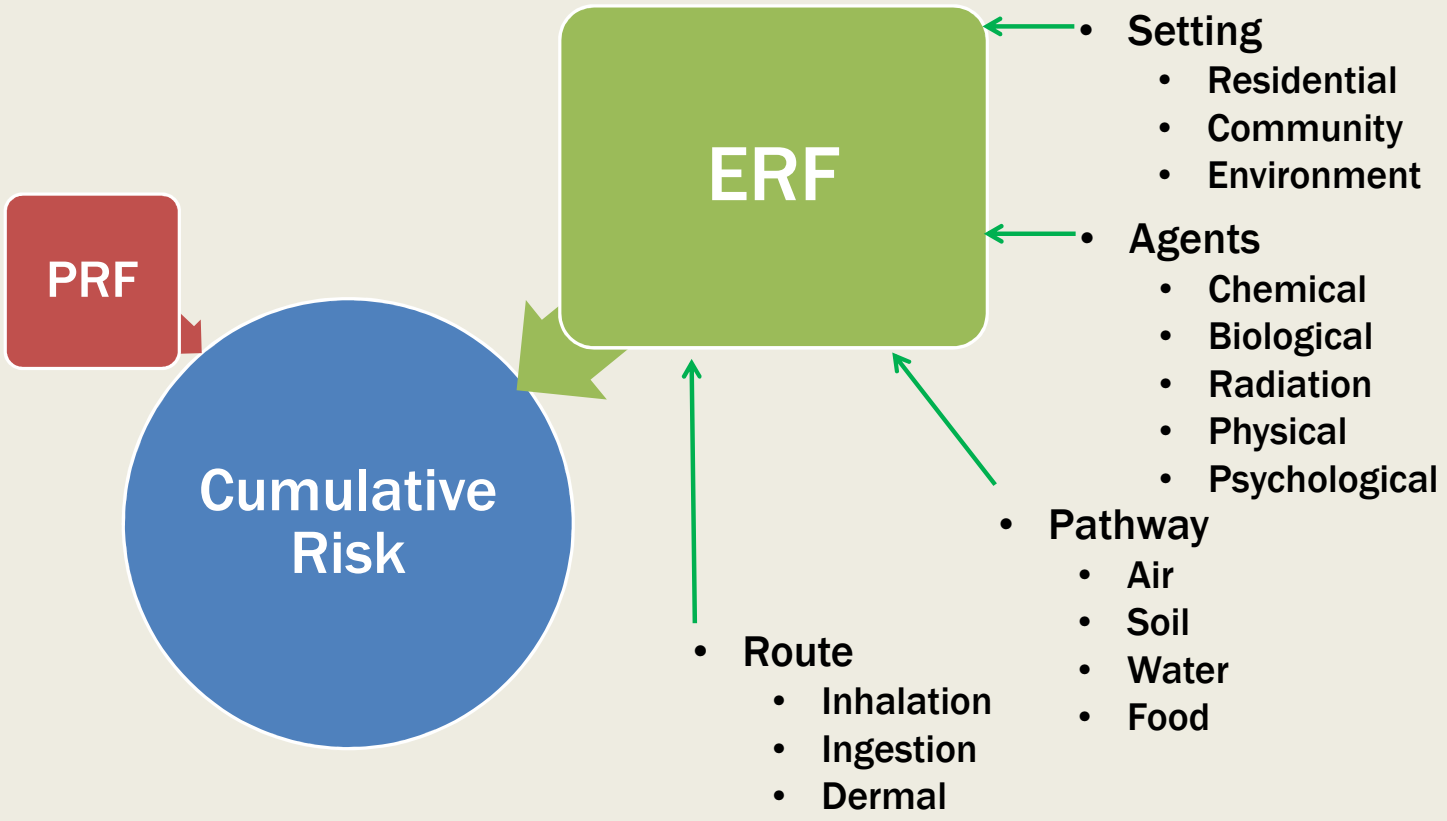
CUMULATIVE RISK ASSESSMENT (CRA)

Environmental Protection Agency (EPA) Definition

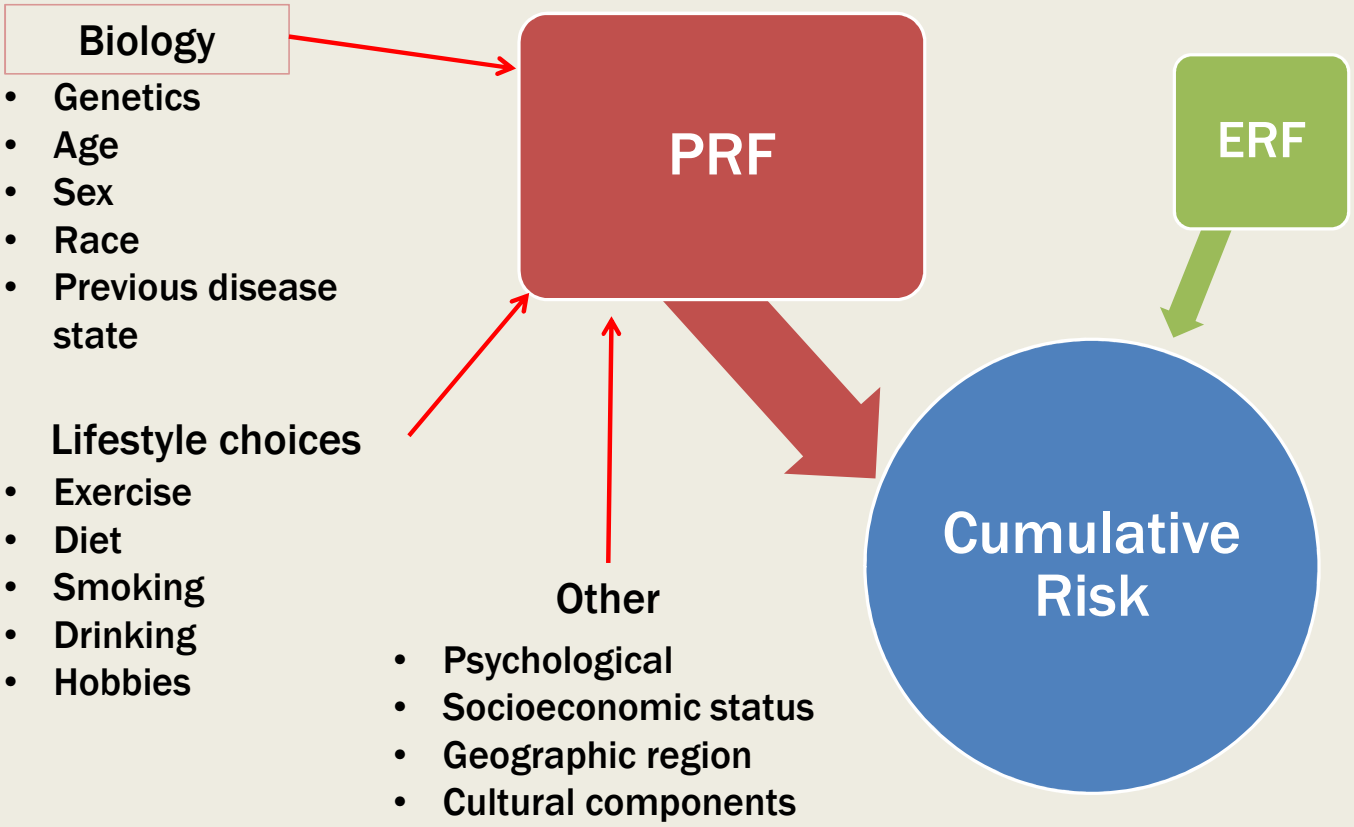
- *"An **analysis, characterization**, and possible quantification **of the combined risks to human health** or the environment **from multiple agents or stressors**."*

CONCEPTUAL MODEL OF CUMULATIVE RISK

ENVIRONMENTAL RISK FACTORS (ERF)

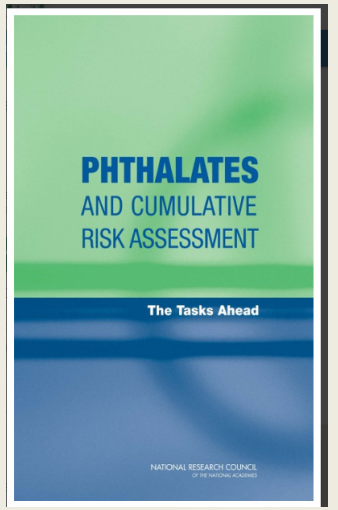


PERSONAL RISK FACTORS (PRF)



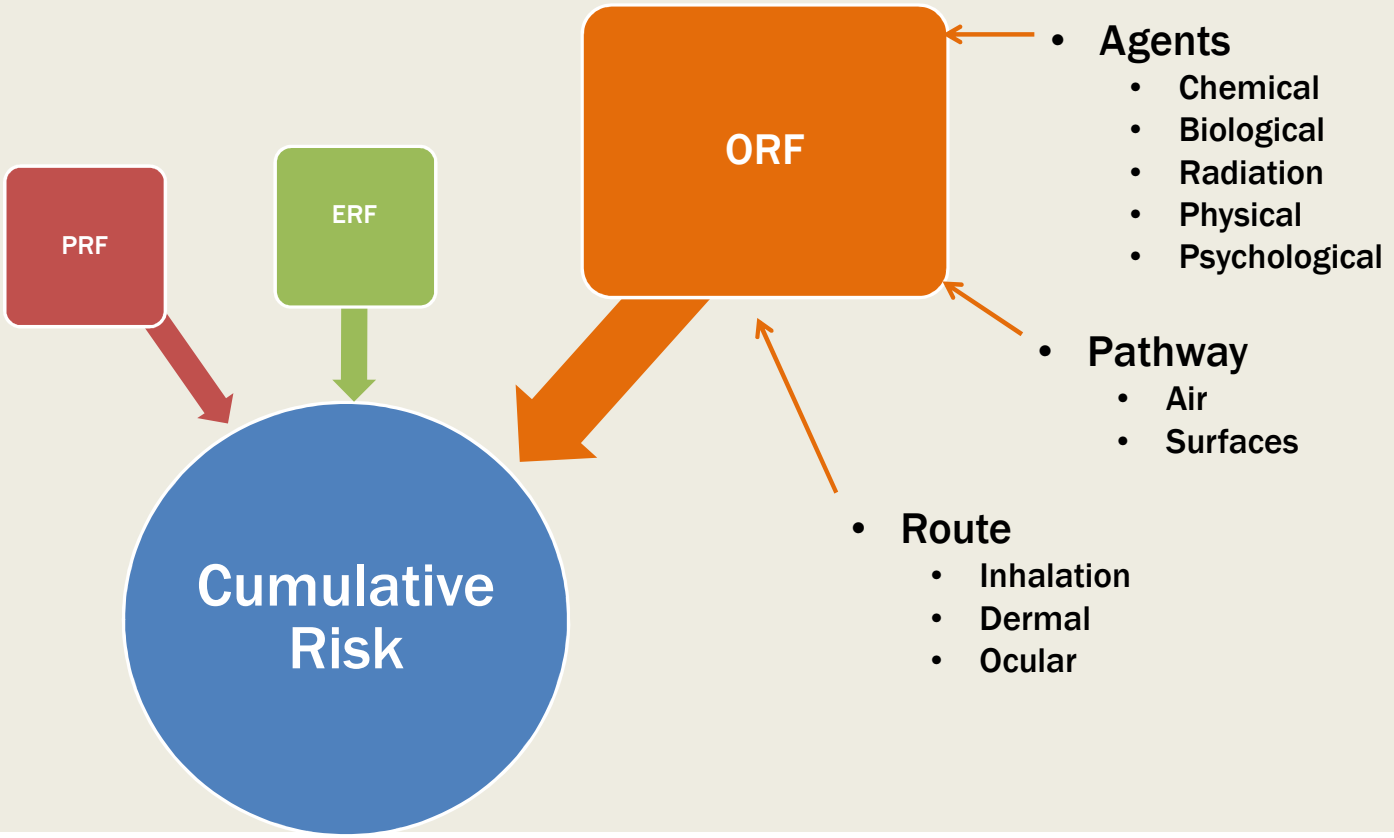
WHAT ABOUT OCCUPATIONAL RISK FACTORS (ORF)?

- Current CRA approaches focus primarily on:
  - Aggregate exposures to chemical classes with common toxic mechanisms
    - Pesticides – Neurotoxicity
    - Phthalates
  - Environmental, community and residential issues
    - Environmental justice
  - EPA and academics



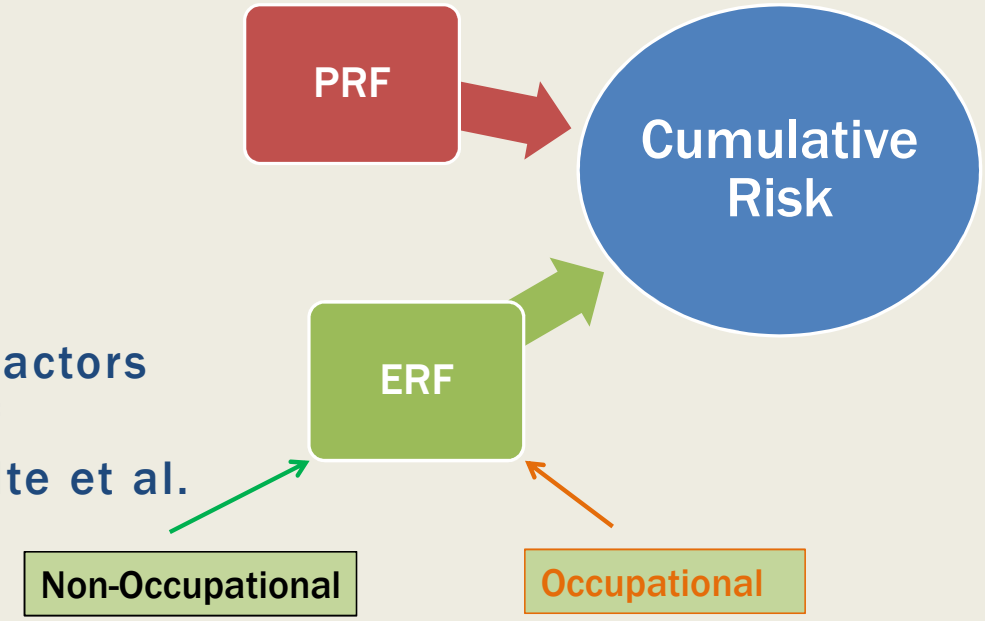
- What about the workplace and occupational risk factors (ORF)?
  - Call for the occupational environment to be considered in CRAs [Fox et al. 2018, Lentz et al. 2015, Pandalai et al. 2013, Williams et al. 2012, Schulte et al. 2012]

MODIFIED CRA MODEL



INTEGRATING CRA & OCCUPATIONAL RISK ASSESSMENT

- ORF impact health & well-being
- Non-ORF influence workers
- Knowledge of the interaction of risk factors may foster enhanced management of occupational illness and injury [Schulte et al. 2012]



CARBON MONOXIDE AND METHYLENE CHLORIDE

- Evidence of additive effect of methylene chloride and carbon monoxide exposure on carboxyhemoglobin levels
- NIOSH Criteria Document on Methylene Chloride [1976]:

$$\frac{C(CO)}{L\ (CO)} + \frac{C(CH2Cl\ 2)}{L\ (CH2Cl\ 2)} \leq 1$$

where:

C(CO) = the TWA exposure concentration of CO

L(CO) = the recommended TWA exposure limit of CO = 35 ppm [135]

C(CH2Cl 2) = the TWA exposure concentration of methylene chloride

L(CH2Cl 2) = the recommended TWA exposure limit of methylene chloride = 75 ppm

CARBON MONOXIDE AND METHYLENE CHLORIDE EXPOSURE

Table V-3

TWA EXPOSURE LIMITS FOR METHYLENE CHLORIDE WHEN CO IS JOINTLY PRESENT IN THE OCCUPATIONAL ENVIRONMENT.

CO TWA	CH_2Cl_2, ppm	
	TWA	Action
0-9	75	37.5
10	54	27
15	43	21.5
20	32	16
25	21	10.5
30	11	5.5
35	0	0

NOISE AND OTOTOXICANTS

- Combined effects of noise and ototoxicants may be additive or greater than additive [OSHA/NIOSH 2018]
  - *"Several studies have suggested that some ototoxic chemicals, such as certain solvents, might exacerbate noise-induced hearing loss even though the noise level is below OSHA's Permissible Exposure Limit (PEL)."*
  - Indicates the importance of recognizing and controlling dermal exposures
  - Highlights the importance of impulse noise
- ACGIH [2018] proposed to add "OTO" notations to chemicals that cause hearing loss alone or in combination with noise exposure (even below 85 dBA)
  - Based on both human and animal data
  - One chemical identified so far in 2018 Notice of Intended Changes list (styrene)
    - Other chemicals listed in text (CO, HCN, lead, ethylbenzene, styrene, toluene, xylene, solvent mixtures)

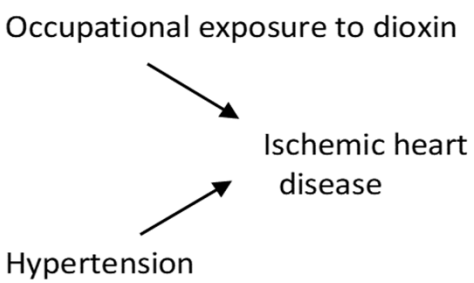
NOISE AND OTOTOXICANTS

Substance Class	Chemicals
Pharmaceuticals **Ototoxicity at therapeutic doses is limited*	Aminoglycosidic antibiotics (e.g. streptomycin, gentamycin) and some other antibiotics (e.g. tetracyclines), Loop diuretics* (e.g. furosemide, ethacrynic acid) Certain analgesics* and antipyretics* (salicylates, quinine, chloroquine) Certain antineoplastic agents (e.g. cisplatin, carboplatin, bleomycin).
Solvents	Carbon disulfide, n-hexane, toluene, p-xylene, ethylbenzene, n-propylbenzene, styrene and methylstyrene, trichloroethylene.
Asphixiants	Carbon monoxide, hydrogen cyanide and its salts, tobacco smoke
Nitriles	3-Butenenitrile, cis-2-pentenenitrile, acrylonitrile, cis-crotononitrile, 3,3'-iminodipropionitrile.
Metals and Compounds	Mercury compounds, germanium dioxide, organic tin compounds, lead.

[OSHA/NIOSH 2018]

OCCUPATIONAL AND PERSONAL RISK FACTORS

A1. A chronic disease and an ORF are independent risks for an adverse health outcome

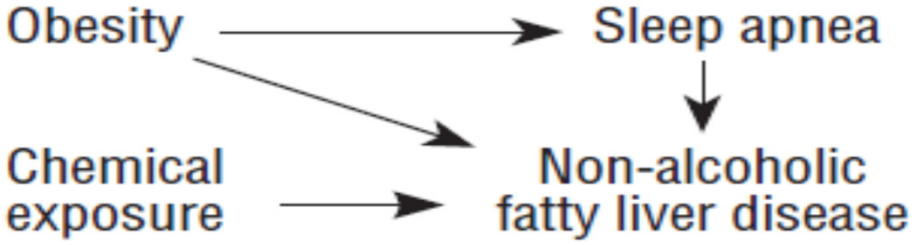


Dioxin may be a risk for ischemic heart disease.

Hypertension is risk for ischemia.

Combined impact may be significant for the development of disease.

1.4 Obesity impacts one outcome, an ORF impacts another, and the two outcomes can be associated with each other



[Schulte et al. 2012, Pandalai et al. 2013]

EXPLORING CUMULATIVE EXPOSURES IN THE WORKPLACE

Method

- Three tiered approach to identify scientific literature with multiple stressors resulting in a clinical health outcome

Tier 1: Screening search strategy

Database search term in PubMed:

Epidemiology or human AND interaction or effect modification AND occupational disease or exposure

Tier 2: Independent screening by expert panel

Inclusion Criteria:

1. English language studies
2. Health effect outcome identified
3. One stressor identified as occupational environment

Exclusion Criteria:

1. Population epidemiology
2. Studies with genetic risk factors
3. Animal studies, reviews, case studies, and other non-research based literature

Tier 3: Review of full reference by expert panel

EXPLORING CUMULATIVE EXPOSURES IN THE WORKPLACE

Results

- Selected literature spans from 1980-2017
- Most studies evaluated 2 exposures (Workplace and Other)
  - Two studies assessed 3 workplace and personal domains
  - The dominant 2nd exposure evaluated was “smoking”
  - Other 2nd exposures were varied and included stressors such as noise, age, saturated fat intake, gender, psychosocial factors
  - Very few studies identified biological exposures, pre-existing health conditions, or job strain/work stress
- Represents various occupations in both manufacturing and service industries

EXPLORING CUMULATIVE EXPOSURES IN THE WORKPLACE

Discussion

- Many different cumulative exposures impacting many types of workplaces and workers exist
- Workplace wellbeing efforts may be helpful (NIOSH Total Worker Health and smoking cessation programs)
- Cumulative risks increase health risks, and are necessary to understand dose- and concentration-response relationships
- Include both modifiable and non-modifiable behaviors and characteristics

Limitations

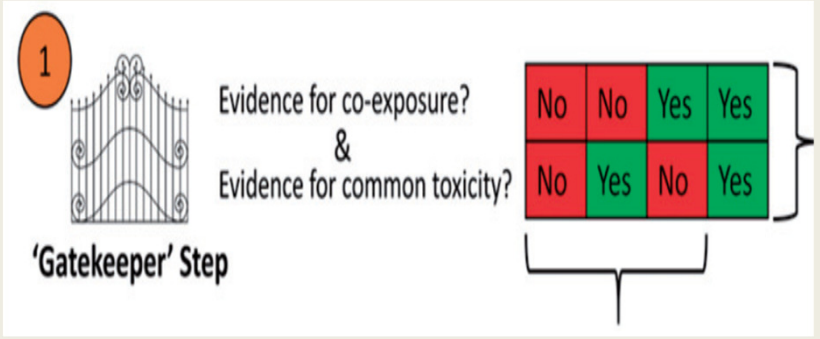
- Strict adverse clinical outcome criterion largely limited results
- Exclusion of population-based studies identifying occupational risk factors *post-hoc*

TOWARDS AN OCCUPATIONAL FRAMEWORK

- How do we begin to address CRA in the workplace?
- Several issues at play
  - Complexity of workplace exposures
  - Temporal issues
  - Lack of easily accessible data
  - “Outside the fenceline” exposures
- EPA [2007] has identified 3 initiating factors that could lead to conducting a CRA:
  - Multiple pollutant sources or releases
  - Elevated concentrations from environmental monitoring or biomonitoring of chemicals
  - Increased population illness in a community

TOWARDS AN OCCUPATIONAL FRAMEWORK

- Gatekeeper step [Moretto et al. 2017]
  - Starting assumption: interactions are unlikely at doses/exposure levels at or below no effect levels
  - Assume dose additivity for chemicals with similar modes of action [Boobis 2011]
  - If a chemical is above health based guidance level, control exposures first before beginning a CRA



(Moretto 2017 Figure 1)

- Problem formulation [Solomon et al. 2016]
  - Purpose, scope, and depth of the assessment
  - Analytical approach and available resources
  - CRAs focus should be stressors or risk factors that have risk management options available [NRC 2009]

TOWARDS AN OCCUPATIONAL FRAMEWORK

Possible approaches:

- Should occupational focused CRAs be on stressors "inside the fence line"/employer's purview?
- Should non-occupational stressors or risk factors only be considered if they are the same as those in workplace or lead to same health effect of concern?
- Should personal risk factors also be considered as they may have important implications from a risk communication/management perspective?
- Stressor based (prospective) vs. health-based (retrospective) designs
- Question: Do the "health-based guidance levels" in the occupational environment (OELs) provide a good starting point for the "gatekeeper step"?
  - Many PELs are out date [OSHA 2018]
  - NIOSH recently updated it's Carcinogen policy to reduce residual risk from 1/1000 to 1/10000 [NIOSH 2016]
  - Other OELs may be outdated- important to evaluate critical health effects of chemicals

WHERE DO WE GO FROM HERE?

Existing Tools

- Mixie (chemical stressor-based approach) [2019]
- Wiser (health effects-based approach) [2019]
- EU Online Interactive Risk Assessment (OiRA) [2019]
- OSHA/NIOSH Preventing Hearing Loss Caused by Chemical (Ototoxicity) and Noise Exposure [2019]
- ACGIH OTO Notations [2018]- Styrene (NIC)
- CRA Training [Society of Risk Analysis meeting 2016, 2017]

FUTURE NEEDS

- Occupational or industry based inventories [Williams 2018] Chemical /non-chemical/personal risk factor linked to combined health effects
  - Conceptual models
  - Multi-stressor exposure databases
  - Occupational exposure factors
- Use of Occupational Exposure Banding?

Health Effects	Chemical Exposures	Other Stressors	Personal Risk Factors
Respiratory	Ammonia, chlorine gas, formaldehyde, isocyanates, cadmium, PM, ozone	Biologicals	Age, obesity, smoking
Heart abnormalities	CO, CO2, hydrogen cyanide, H2S, methylene chloride	Heat, shift work	Cardiovascular disease
High blood pressure	Lead	Stress, shift work	Smoking, obesity
Hearing loss	Solvents, lead, CO	Noise	Age
Visual impairment	Methanol	Non-ionizing radiation, poor lighting, stress	Age, alcohol, diabetes
Skin effects	Hydrogen fluoride, PCB/ TCDD, tin, cobalt, aluminum	Solar radiation, Non-ionizing radiation	Smoking
Neurotoxicity	Solvents, metals	Biologicals, stress	Age
Lung cancer	Asbestos, silica, metals	Biologicals, ionizing radiation	Smoking

[Williams 2018]

FOR MORE INFORMATION

- **NIOSH Cumulative Risk Assessment Mini- Symposium (recorded 7/31/18)- Available through NIOSH Science Blog (https://blogs.cdc.gov/niosh-science-blog/2018/11/26/cra/)**

Presenter	Affiliation	Topic	Time Slot
Dr. John Howard	NIOSH	Introductory Remarks	9:00 A.M.—9:10 A.M.
Dr. Glenn Rice	US EPA	Cumulative Risk Assessment: Asking the Right Questions	9:10 A.M.—9:35 A.M.
Mr. Frank Hearl	NIOSH	NORA Mixed Exposures: 20th Year Progress Report	9:35 A.M.—10:00 A.M.
Dr. Sudha Pandalai & Dr. Paul Schulte	NIOSH	The interrelationship of occupational and personal risk factors: building block in cumulative risk assessment	10:00 A.M.—10:25 A.M.
Break	Break	Break	10:25 A.M.—10:35 A.M.
Dr. Jane Clougherty	Drexel University	Merging Chemical and Psychosocial risk factors in CRA	10:35 A.M.—11:00 A.M.
Dr. Thais Morata	NIOSH	Addressing Physical Stressors in Cumulative Risk Assessment: Noise as an example	11:00 A.M.—11:25 A.M.
Dr. Pamela Williams	E Risk Sciences, LLP	CRA in Practice: What can NIOSH and the IH Community do to help?	11:25 A.M.—11:50 A.M.
Speaker Forum Discussion			11:50 A.M.—12:30 P.M.

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- Thais Morata, NIOSH
- Sudha Pandalai, NIOSH
- Glenn Rice, EPA
- Alan Rossner, Clarkson University
- Miriam Siegel, NIOSH
- Paul Schulte, NIOSH
- Pamela Williams, E Risk Sciences, LLC
- Vanessa Williams, NIOSH

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QUESTIONS?

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