Evaluating hypothetical limits on metalworking fluid exposure for reducing non-Hodgkin lymphoma incidence

An application of the hazard-extended parametric g-formula

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Non-Hodgkin Lymphoma

- 7th most common cancer in the US
- Incidence rose dramatically 1960 to 1990 around the world
  - In the US: 8.5 to 18.3 per 100,000 between 1973 and 2019
- Strongest risk factors[1]
  - Immunosuppression, both genetic and acquired
  - Infection by *H. pylori*, Epstein-Barr virus, Hepatitis C virus, HIV
- Known risk factors account for about 50% of observed incidence[2]

NHL and peseticides

- Rise in NHL mirrors rise in chemicalization of agriculture, industry, and warfare[3]
  - Agricultural exposure to pesticides very well studied
  - Meta-analyses yielded consistent associations with pesticides: carbamate, organophosphorous, triazine, organochlorine[4]

Soluble MWF

- Water-based soluble MWFs contain diverse additives:
  - Triazines: biocides
  - Nitrites: rust inhibitors
  - Sulfonates: emulsifiers
  - Organochlorines: extreme pressure performance enhancers
- In UAW-GM, soluble MWF was used more frequently and in much larger quantities than straight and synthetic MWF
- Globally, soluble MWF is the most common

MWF exposure in UAW-GM

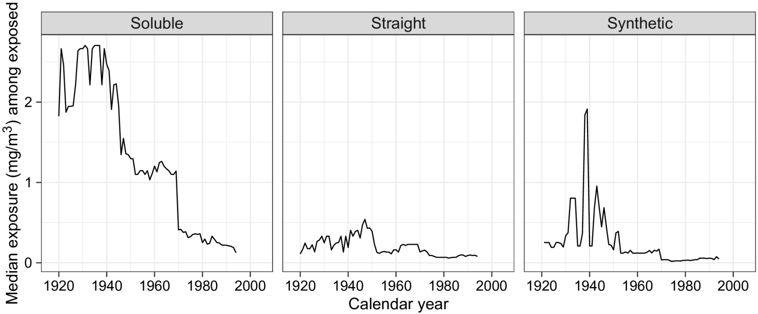

Figure 1: Median average annual exposure among exposed workers over time.

- 89% ever exposed to soluble
- 57% ever exposed to straight
- 35% ever exposed to synthetic

MWF exposure and NHL in UAW-GM

N)

Exposure Category	No. of Cases	HR (95% CI)
0 to 0.05	54	
> 0.05 to 3.04	113	1.40 (0.98, 2.00)
> 3.04 to 11.1	113	1.49 (1.02, 2.17)
> 11.1	113	1.70 (1.13, 2.54)
Total	393	

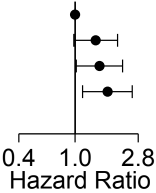

Figure 2: NHL and soluble MWF exposure in recent cancer incidence analysis (Hilary's paper, in press).

Iterated conditional expectation (ICE) g-formula

ICE g-formula estimators rely on the tower property of expectation (from law of total probability)

- For example, $\mathbb{E}\,\mathbb{E}\left[Y \mid A = \check{a}, W\right] = \mathbb{E}\left[Y \mid A = \check{a}\right]$
- For discrete W, we have
  $\mathbb{E}\left[Y \mid A = \check{a}\right] = \sum_{w \in \mathcal{W}} \mathbb{E}\left[Y \mid A = \check{a}, W = w\right] \mathbb{P}\left(W = w\right)$
  This is the non-parametric g-computation result, which we can estimate parametrically by specifying a model:
  $$\mathbb{E}\left[Y \mid A = \check{a}, W = w\right] = \beta_0 + \beta_1 \check{a} + \beta_2 w$$
  - Avoids the need for propensity score
  - Relies heavily on correct model specification
  - Equivalent to model-based standardization

ICE g-formula for multiple timepoints

$$
\begin{aligned}
&\text{Put} \quad \psi = \mathbb{E}_{f_{Y_J}}\left[Y_J(1 - Y_{J-1}) \mid \bar{L}_J, \bar{A}_J = \bar{A}^g_J, \bar{Y}_{J-1} = C_J = 0\right] \\
&\text{Put} \quad \psi = \mathbb{E}_{f_{L_J}}\left[\psi \mid \bar{L}_{J-1}, \bar{A}_{J-1} = \bar{A}^g_{J-1}, \bar{Y}_{J-1} = C_J = 0\right] \\
&\text{Put} \quad \psi = \mathbb{E}_{f_{Y_{J-1}}}\left[Y_{J-1}(1 - Y_{J-2}) + \psi \mid \bar{L}_{J-1}, \bar{A}_{J-1} = \bar{A}^g_{J-1}, \bar{Y}_{J-2} = C_{J-1} = 0\right] \\
&\qquad\quad \vdots \\
&\text{Put} \quad \psi = \mathbb{E}_{f_{Y_1}}\left[Y_1 + \psi \mid L_1, A_1 = A^g_1, \bar{Y}_0 = C_0 = 0\right]
\end{aligned}
$$

$$
\rightsquigarrow \qquad \mathbb{E}\left[Y^g_J\right] = \mathbb{E}_{f_{L_1}}\left[\psi\right]
$$

For *hazard-extended* ICE g-formula,

we use discrete hazard estimate for interval $(j-1, j]$ in place of Y_j

Intervention of interest

- Deterministic stochastic interventions: limit soluble MWF to
  - 0.5 mg/m^3 (NIOSH REL)
  - 0.25 mg/m^3
  - 0.05 mg/m^3
- Dynamic stochastic interventions: reduce soluble MWF such that total MWF exposure limited to 0.5, 0.25, and 0.05 mg/m^3
  - Translates to the following exposure limits on soluble MWF:
    - $\max(0,\ 0.5 - \text{str} - \text{syn})$
    - $\max(0,\ 0.25 - \text{str} - \text{syn})$
    - $\max(0,\ 0.05 - \text{str} - \text{syn})$

Illustration of interventions when applied

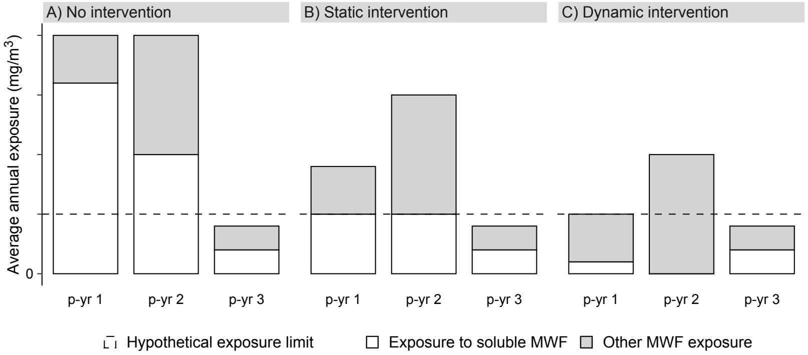

Figure 3: Observed and post-intervention levels of exposure in three example person-years.

Results

Exposure limit on soluble MWF (mg/m^3)	Person-years intervened (%)	Risk per 1000	(risk 95% CI)	RR	(RR 95% CI)
None	0.0	9.56	(8.15, 10.89)	1.00	
0.5	23.8	8.30	(6.52, 10.19)	0.87	(0.72, 1.02)
0.25	36.2	8.06	(6.15, 10.15)	0.84	(0.68, 1.01)
0.05	43.9	7.52	(5.73, 9.51)	0.79	(0.62, 0.97)
max(0, 0.5 – str – syn)	28.3	8.00	(6.27, 9.87)	0.84	(0.69, 0.99)
max(0, 0.25 – str – syn)	40.0	7.69	(5.88, 9.64)	0.80	(0.64, 0.98)
max(0, 0.05 – str – syn)	52.8	6.89	(4.62, 9.75)	0.72	(0.48, 1.01)

Discussion

- Assumption of correct model specification is doing heavy duty
  - Trade-off between satisfying positivity and correct model specification
  - But approach is much more flexible than Cox PH
- Why bother with stochastic intervention?
  - In reality, companies may not reduce exposures already below REL
  - In estimation, we can achieve positivity more easily
- Why bother with complex *dynamic* stochastic intervention
  - NIOSH REL is for total MWF exposure?
  - Dynamic interventions can achieve risk reductions by intervening on fewer person-years (analytically) and processes (in reality)

Citations

1. Ekström-Smedby K. Epidemiology and etiology of non-Hodgkin lymphoma–a review. *Acta oncologica*. 2006;45(3):258-271.
2. Hartge P, Devesa SS. Quantification of the impact of known risk factors on time trends in non-hodgkin's lymphoma incidence. *Cancer research*. 1992;52(19_Supplement):5566s-5569s.
3. Nelson NJ. Studies examine whether persistent organic agents may be responsible for rise in lymphoma rates. *Journal of the National Cancer Institute*. 2005;97(20):1490-1491.
4. Schinasi L, Leon ME. Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*. 2014;11(4):4449-4527. doi:10.3390/ijerph110404449.