



REVIEW OF EVIDENCE ON SHAPE OF $PM_{2.5}$ CONCENTRATION-RESPONSE FUNCTIONS

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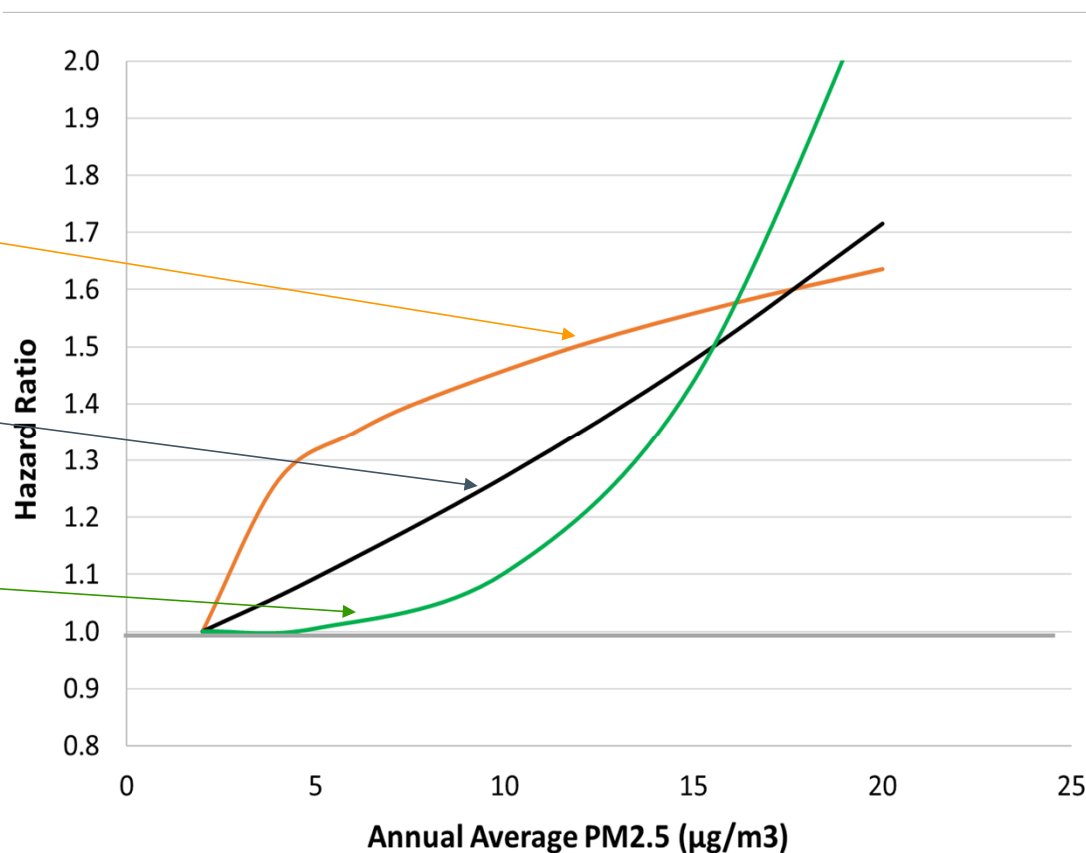
Concentration-Response (C-R) “Shape”

--Terminology and Policy Relevance

“Supralinear”: risk per *incremental* unit of exposure is larger at lower concentrations

“Linear”: risk per *incremental* unit of exposure is same for all exposure levels

“Sublinear”: risk per *incremental* unit of exposure is larger at higher concentrations



- The linear shape is assumed in most of the PM_{2.5} epi literature
- Growing set of studies use more complex statistical methods to assess non-linearity of the C-Rs
- Shape can inform a decision on the appropriate level for a NAAQS

In 2018, Detailed Review of Growing Literature on PM_{2.5} C-R Shape Summarized in My Submitted Comments on Draft ISA

Conclusions:

- Shapes detected in this literature show no clear pattern
- ISA correctly recognized that recent studies reporting supralinear C-Rs are counterbalanced by sublinear C-Rs reported for same effects categories
- Confidence intervals around C-R curves very wide as levels approach lowest measured levels (LMLs) — indicating great uncertainty on shape at those levels

Summary of Shapes in Papers in 2018 Draft ISA

1st Author	Year	Shape Reported	Cohort	Health Endpoint
Crouse	2015	supralinear	CanCHEC-1991	LT mort
Pinault	2016	supralinear	CCHS	LT mort
Crouse	2012	supralinear	CanCHEC-1991	LT CV mort
Weichenthal	2014	supra (but inverted U shape) for men only ; null for women	Agricultural Health Study	LT CV mort
Jerrett	2017	supralinear	ACS	LT Circulatory mort
Di	2017b	supralinear	Medicare	ST mort
Lepeule	2012	linear	Harvard 6 Cities	LT mort
Di	2017a	linear	Medicare	LT mort
Lepeule	2012	slightly supralinear	Harvard 6 Cities	LT CV mort
Thurston	2016	mixed/linear overall	NIH-AARP	LT CV mort
Crouse	2012	sublinear	CanCHEC-1991	LT mort
Villeneuve	2015	sublinear (but U-shaped with downward slope in range <9)	Can women (NBSS)	LT mort
Thurston	2016	sublinear	NIH-AARP	LT mort
Chen	2016	sublinear	EFFECT (AMI survivors)	LT mort
Shi	2016	sublinear	Medicare-NewEng	LT mort
Villeneuve	2015	sublinear	Can women (NBSS)	LT CV mort
Shi	2016	sublinear	Medicare-NewEng	ST mort

2021 Supplemental ISA Identifies Much More Literature on PM_{2.5} C-R Shape, Which I Have Also Closely Reviewed

Conclusions:

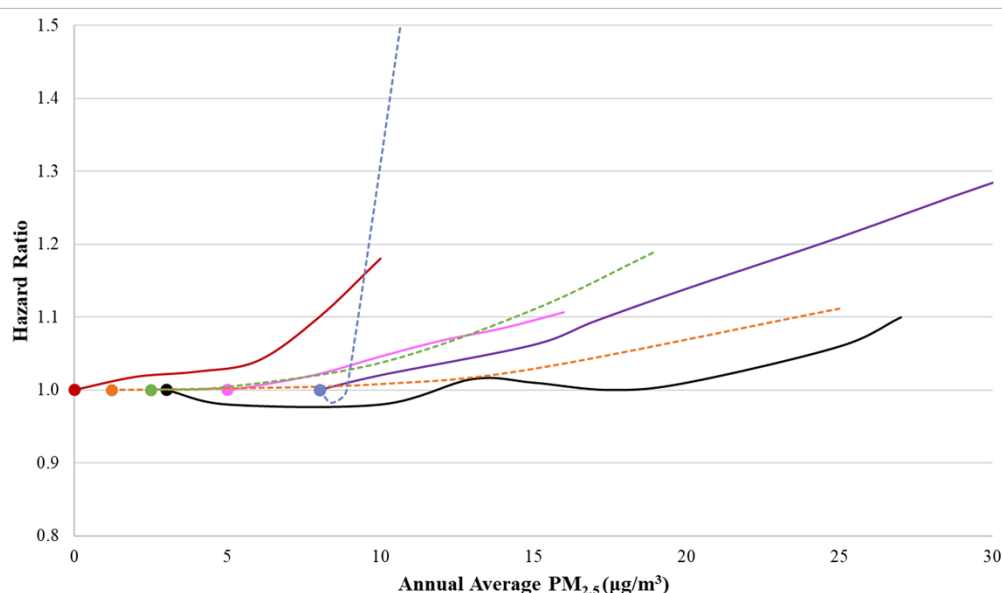
- We remain in much the same situation as 4 years ago
- Still no clear evidence on C-R shape
- Draft Supplemental ISA continues to correctly recognize that recent supralinear C-R evidence is counterbalanced by reported sublinear C-Rs for same effects categories

Summary of Shapes in Papers in Draft 2021 Supplemental ISA

1st Author	Year	Shape Reported	Cohort	Health Endpoint
Pappin	2019	supralinear	CanCHEC 1991,1996,&2001	LT non-acc mort
Christidis	2019	supralinear	CCHS	LT non-acc mort
Pinault	2017	supralinear	CanCHEC 2001	LT non-acc mort
Pinault	2017	supralinear	CanCHEC 2001	LT CV mort
Lavigne	2018	slightly supralinear although ISA says "linear"	24 cities in Canada	ST non-acc mortality
Bai	2019	supralinear	ONPHEC-Ontario	LT CV morbidity
Danesh Yazdi	2019	slightly supralinear although ISA says 'generally linear"	Medicare-SE	LT CV morbidity (stroke)
Pope	2019	linear (slightly sub)	NHIS	LT CV mort
Loop	2018	linear(v. insignif)	REGARDS	LT CV mort
Liu	2019	mixed/linear overall	25 cities in Canada	ST non-acc mortality
Liu	2019	Too uncertain < 8 to assess shape but generally linear >8	107 cities in US	ST non-acc mortality
Bai	2019	linear	ONPHEC-Ontario	LT CV morbidity
Chen	2020	linear	ONPHEC-Ontario	LT CV morbidity
Shin	2019	linear	ONPHEC-Ontario	LT CV morbidity
Danesh Yazdi	2019	linear <14	Medicare-SE	LT CV morbidity (MI)
Loop	2018	null (linear negative slope)	REGARDS	LT CV morbidity
Loop	2018	null (linear negative slope)	REGARDS	LT CV morbidity
Zhang	2021	sublinear	Ontario Health Study	LT non-acc mort
Pope	2019	sublinear	NHIS	LT non-acc mort
Ward-Caviness	2020	sublinear (ISA Table 3-6 says linear but is only approx linear for	HF patients-NC	LT non-acc mort
Wang	2020	sublinear although ISA says "linear"	Medicare	LT non-acc mort
Zhang	2021	sublinear	Ontario Health Study	LT CV mort
Chen	2020	sublinear	ONPHEC-Ontario	LT CV mort
Wang	2020	sublinear	Medicare	LT CV mort
Shin	2019	sublinear	ONPHEC-Ontario	LT CV morbidity
Lavigne	2019	but statistically insignif over entire range presented (<10)	24 cities in Canada	ST CV mortality

Graphical Summary of C-R Shapes for Non-Accidental Long-Term Mortality (2018 and 2021 ISA Papers Combined)

US Ambient Air

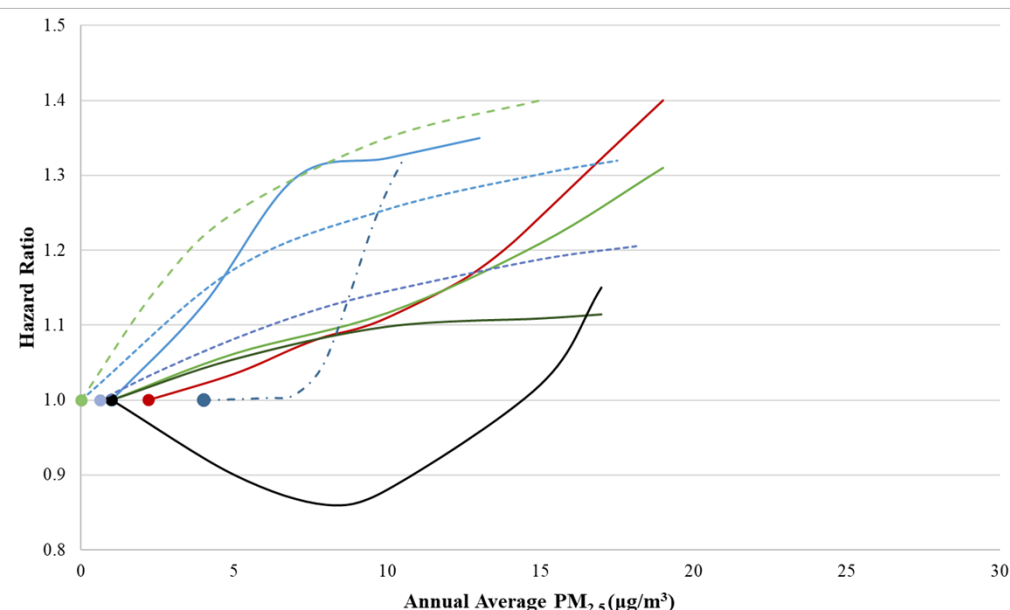


Notes:

1. All curves approximated by NERA.
2. The dot on the left end of each curve indicates location of that study's LML.
3. Relative risk re-scaled for Lepeule (2012) and Thurston (2016).
4. Shi (2016) and Lepeule (2012) are all-cause mortality. Lepeule PM 30 to 40 not shown.

Di (2017a)
 Lepeule (2012)
 Thurston (2016)
 Shi (2016)
 Wang (2020)
 Pope (2019)
 Ward Caviness (2020) - Modeled $PM_{2.5}$ Data

Canadian Ambient Air



Notes:

1. All curves approximated by NERA (refined 12-10-18)
2. The dot on the left end of each curve indicates location of that study's LML.
3. Relative risk re-scaled for Crouse (2012), Crouse (2015), Pinault (2016), and Villeneuve (2015).

Chen (2016)
 Crouse (2015)
 Villeneuve (2015)
 Pappin (2019) - SCHIF Pooled
 Zhang (2021)
 Crouse (2012)
 Pinault (2016)
 Christidis (2019) - SCHIF
 Pinault (2017)

The New Canadian Studies in the 2021 Supplemental ISA Provide All but One of the New Reports of Supralinear Shape, *BUT*:

- Of the papers that evaluate multi-pollutant models:
 - These Canadian papers also report that their estimates of PM_{2.5} relative risks become much lower, often null, when estimated in multi-pollutant linear models
 - This finding arises for several Canadian cohorts studied in these papers
- Despite the simultaneous evidence that the Canadian PM_{2.5} relative risk estimates are strongly diminished in multi-pollutant models, the only PM_{2.5} C-R *shape* estimates they report are based on single-pollutant (*i.e.*, PM_{2.5}-only) models
- Many uncontrolled factors may be influencing PM_{2.5} C-R shape estimates
 - C-R shape in one region may not apply in other regions, to the extent that these other factors differ regionally
 - This point has been explicitly recognized in Pinault *et al.*, 2017

Bottom Line

- Shapes detected to date reveal no clear pattern and could reflect mere statistical randomness from study to study
- New studies referenced in the Draft Supplemental ISA do not alter this conclusion
- Growing evidence, however, that shape estimates may differ by airshed or population in still-unknown ways
 - i.e.*, we cannot simply extrapolate from Canadian shapes to the US
- Better understanding of true shape even in a given region will require sensitivity analyses that simultaneously control for co-pollutants or other local risk factors while performing non-linear estimations of PM_{2.5} C-R shapes

At this point, there is insufficient information for using any shape evidence in forming policy judgments