Remarks on Integrated Science Assessment External Review Draft to Be Presented to CASAC During Its Meeting on December 12, 2018

Anne E. Smith, Ph.D.
NERA Economic Consulting

Prepared on behalf of Utility Air Regulatory Group
December 5, 2018

1. Background and Focus of These Remarks

On October 23, 2018, EPA released its external review draft of the Integrated Science Assessment (ISA) for Particulate Matter (PM). Comments, which are due to be submitted to the docket by December 11, 2018, may be summarized orally during the public comments segment of the Clean Air Scientific Advisory Committee (CASAC) meeting on December 12, 2018. To assist CASAC members in preparing for that meeting, individuals intending to speak before CASAC have been asked to submit copies of their presentation materials by December 5. In response to this request, this document provides an overview of key points that the author intends to present to CASAC. The points herein will be more completely developed in written comments that will be submitted to the docket on December 11, 2018.

The ISA, at nearly 2,000 pages in length, covers a wide range of issues of relevance to the setting of both primary and secondary national ambient air quality standards (NAAQS) for PM, including fine PM ($PM_{2.5}$). This set of comments focuses on what the ISA reports on evidence regarding a specific policy-relevant question: *the shape of the $PM_{2.5}$ concentration-response (C-R) relationship*. This evidence is summarized for mortality risk C-R relationships, for all nonaccidental deaths and for deaths attributed to cardiovascular disease (CVD). Most of the C-R evidence is derived from studies of long-term $PM_{2.5}$ exposure, but the ISA also summarizes a few studies addressing the potential shape of a C-R function for acute $PM_{2.5}$ exposure. The acute risk studies in the ISA are all for all-cause mortality; none are for CVD mortality risk.

In general, the ISA finds that among recent (2009-2018) epidemiological studies that provide any indication of potential C-R shape, most conclude that the null hypothesis of linearity across the range of observed $PM_{2.5}$ concentrations cannot be rejected. The ISA notes that some recent studies have suggested the possibility of an increasing C-R slope at lower concentrations, which is often referred to as "supralinearity." However, the ISA does not appear to assign much weight to findings of supralinearity.

These comments support the caution with which the ISA addresses the evidence of supralinearity in C-R shape. We review the papers cited in the sections of the ISA discussing C-R shape, identify a few additional papers that contain evidence on C-R shapes that are not currently cited in those sections, and provide a synthesis of these papers that we believe underscores the appropriateness of caution in making any conclusions on C-R shape at this time. In brief, when the various C-R relationships estimated in the cited papers are compared in an apples-to-apples format, the primary finding would seem to be a lack of consistency in their shapes. While many results are described by the authors (and by the ISA) as "linear," the actual C-R relationships reported in the papers take on a variety of shapes, from sublinear to supralinear. In this context, the evidence of supralinearity appears to be just one end of a spectrum of shapes that have been estimated, with little reason to separate any of them out as more indicative of the "true" C-R shape rather than simply a manifestation of the significant uncertainty on shape that is inherently difficult to resolve using the tools of population-wide epidemiology.

The ISA contains references to several non-U.S./non-Canadian epidemiological studies. These comments do not include these papers in its syntheses for two reasons. The first is that we believe it is important that a comparison of available evidence on shape for a particular region include all known papers that explored shape, regardless of their results. While we feel we are able, within the available time, to assess the ISA's completeness in representation of the relevant U.S. and Canadian papers, we do not have such confidence for the literature world-wide. Second, given the possibility that varying toxicities of the PM mix in different regions may result in different C-R shapes, results from entirely different parts of the world could confuse rather than refine the ability to detect policy-relevant patterns. In fact, we will show that this could be a concern even for use of Canadian studies, and we separate our summary of results in Canadian papers from those in U.S. papers. We believe the ISA should also give less weight to the European papers, particularly on the question of C-R shape.

2. The Basics of Estimating the Shape of the C-R Relationship

Much of the epidemiological evidence on long-term C-R relationships has been derived from parametric estimation methods such as Cox Proportional Hazards (CPH) analysis. A standard CPH analysis produces a single estimate of the slope of the C-R relationship that is invariant with respect to the exposure level. Efforts to explore the shape of the C-R relationship are effectively efforts to determine whether the slope of the C-R relationship varies with the exposure level. This is done by any of a variety of methods, but the most commonly used method found in the recent literature summarized in the ISA is a smoothing method called "splines."

Graphs must be used to present results on C-R shape because the results of the spline-based nonlinear estimation methods most of these studies have applied cannot be readily summarized with a few parameter estimates, as can be done for the estimates resulting from a standard CPH analysis. Thus, the comments that follow rely heavily on graphical comparisons of results of different studies rather than summary tables.[1]

3. Synthesis of C-R Evidence Cited in ISA

Shapes of Long-term Nonaccidental Mortality C-R Relationships Cited in the ISA

ISA Section 11.2.4 provides a review of the papers that consider possible shapes for long-term C-Rs for nonaccidental mortality risk from $PM_{2.5}$, which are summarized in Table 11-7. It accounts for 5 Canadian papers[2] and 5 U.S. papers.[3] All but one of these papers (Hart et al., 2015) presents graphs of their preferred estimate of the C-R relationship. The ISA provides some examples of those graphs in Figures 11-22 and 11-23, which show a wide variety of shapes. However, those figures are reported in different relative risk units, with different reference points, and on very different scales. While the scales have been selected by their respective authors to best represent their individual C-R curve estimate, it is not easy for a reader of the ISA to understand how these results compare and contrast to each other. A distinctive shape in one graph may appear much like all the rest when restated in comparable units.

Figure 1 presents the curves (without their associated confidence intervals) for the 4 U.S. papers that contain such graphs, and Figure 2 presents the curves for the 5 Canadian papers. (Figures appear at the

[1] We have had to make our own approximations of the shapes in the original papers in order to consolidate them into a single chart to enable the inter-study comparisons that are a part of these comments. There may thus be some minor differences in the figures in these comments and those in the original studies, but we believe that any inaccuracies in our graphical approximations, if they are evident at all, will not affect any of the points that we make in these comments.

[2] Chen et al. (2016); Crouse et al. (2012); Crouse et al. (2015); Pinault et al. (2016); Villeneuve et al. (2015).

[3] Di et al. (2017a); Hart et al. (2015); Lepeule et al. (2012); Shi et al. (2016); Thurston et al. (2016).

end of this document.) In both figures, the curves provided in the original papers have been rescaled where necessary so that all have the following consistent presentation. The y-axis is stated as relative risk, and the curves are graphed to show their risk relative to the lowest measured level (LML) of $PM_{2.5}$ in each respective study.[4] That LML's value is indicated by a circle at the left-hand end of each curve. (It always sits at 1.0 on the y-axis, given our construction of the LML as the point of reference.) The curves are not continued to levels below their LML, as that would represent an extrapolation outside of the observations defining each C-R curve.

These two figures show a range of shapes, with relatively substantial differences in estimates of shape across the Canadian papers. Supralinearity does appear among the Canadian papers, but it is not among the U.S. papers:

- Two of the 4 U.S. papers (Shi et al. and Thurston et al.) present best fit shapes that are sublinear (even though the ISA reports that Thurston et al. "observed [a] linear relationship"). The other 2 of the 4 U.S. papers present C-R curves that are essentially linear (Lepeule et al., and Di et al.)

- Two of the 5 Canadian papers present shapes that are sublinear (Chen et al., and Villeneuve et al.), even though Chen et al. state that they found no "departure from linearity," which appears to be a statement that the somewhat sublinear shape that they present is not *statistically significantly* different from linear. Two of the 5 Canadian papers (Pinault et al., 2016, and Crouse et al., 2015) present shapes that are supralinear. The notably high degree of supralinearity appears in the paper by Pinault et al. (2016).[5] The remaining paper presents a best-fit shape that has both sublinear and supralinear aspects, although neither portion of the C-R shape is dramatically different from linear (and the authors report it is not statistically significantly different from a curve that assumes linearity).

Shapes of Long-term Cardiovascular Mortality C-R Relationships Cited in the ISA

ISA Section 6.2.16 provides a review of the papers that consider possible shapes for long-term C-Rs for cardiovascular mortality risk from $PM_{2.5}$, which are summarized in Table 6-52. That table accounts for 3 Canadian papers[6] and 4 U.S. papers.[7] All but one of these papers (Gan et al., 2011) presents graphs of their preferred estimate of the C-R relationship's shape.[8] The ISA provides just two examples of those graphs in Figures 6-26 and 6-27. As for nonaccidental mortality risk, we have graphed all of the curves in common units. Figures 3 and 4 (at the end of the document) present U.S. and Canadian shapes, respectively, for those C-R shapes that are specific to CVD or circulatory mortality. Again, these two figures show a range of shapes:

---

[4] All C-R curves report risk *relative* to an arbitrary reference point within the range of observations. There appears to be no standard practice for which observation is used as the reference point, with some papers placing the reference point at or near the mean concentration in the observed data and some at the LML. To enable comparability across reported C-R curves, we have scaled all of the reported curves to have their respective LMLs as the reference point. Those curves that have been rescaled from the original document are identified in the figure notes.

[5] All of the other papers shown in Figures 1 and 2 use natural splines, although two use a penalized splines method that constrains the natural spline to always be monotonically (i.e., smoothly) increasing, and one uses a two-dimensional extension of natural splines (called a "thin plate spline") to estimate a joint C-R for both $PM_{2.5}$ and ozone. Pinault et al. (2016) uses an R function called "smoothHR" that searches for the best spline fit.

[6] Crouse et al. (2012); Gan et al. (2011); Villeneuve et al. (2015).

[7] Jerrett et al. (2017); Lepeule et al. (2012); Weichenthal et al. (2014); Thurston et al. (2016).

[8] Again, graphs are used because nonlinear estimation methods cannot be readily summarized with a few numerical parameter estimates.

- Two of the 4 U.S. shape estimates (Lepeule et al. and Thurston et al.) are linear. One paper (Jerrett et al.) finds a classically supralinear shape. The fourth (Weichenthal et al.) might be described as supralinear, but it actually has a negative slope, and one must ask whether this is evidence of supralinearity or data that are inconsistent with dose-response more generally.

- Of the 2 Canadian CVD estimates, one is sublinear and one is supralinear.

Shapes of Short-term Mortality C-R Relationships Cited in the ISA

Section 11.1.10 of the ISA addressed recent evidence on C-R shape for short-term exposure, or acute risk, citing three papers.[9] All three are based on U.S. populations and address all-cause mortality. Figure 5 (at the end of this document) presents the shapes of the estimated acute C-R relationships for the two papers that provide such shape estimates (Shi et al., and Di et al.). These use the same relative risk scale on the y-axis as for the long-term mortality risk figures but expand the x-axis to higher $PM_{2.5}$ concentrations to reflect that daily concentrations in acute studies vary more widely than the annual averages used in long-term studies. The truncation of the Shi et al. curve at 30 $\mu g/m^3$ reflects that fact that the Shi et al. curve was estimated only on the subset days in that study's dataset for which 24-hour average $PM_{2.5}$ was less than 30 $\mu g/m^3$. In that sense, the two curves are not exactly comparable to each other. With that limitation in mind, we note that the available curves in this endpoint category again indicate different types of C-R shapes: one is either sublinear or nearly linear (Shi et al.) while the other indicates supralinearity (Di et al.).

The third paper (Lee et al.) did not estimate a C-R shape, but instead first applied standard CPH estimation to the entire range of $PM_{2.5}$ concentrations and then applied CPH to the subset of days where $PM_{2.5}$ concentrations were below the current NAAQS. The CPH-based slope estimate for the full range of $PM_{2.5}$ was lower than that for the lower-$PM_{2.5}$ subset of exposures, and this is construed as evidence of supralinearity, even though it does not indicate what that shape looks like as a function of PM.

4. Papers Reporting Evidence on C-R Shapes Not Cited in ISA

The section above has summarized the key recent evidence on C-R shape mentioned in the ISA, focusing on long-term and short-term nonaccidental/all-cause risk, and on long-term CVD risks. In conducting our review of the ISA, we relied on our own database of epidemiological studies to determine whether the ISA has been thorough. In general, we have found this to be the case for papers that have relied on some form of smoothing such as splines. However, we have identified a few papers not cited that have reported results using the subcategorization method to test for possible nonlinearities and two papers using a relatively new method devised specifically to assess alternative shapes. The latter papers present the more significant gap in the ISA review and are thus discussed first in this section.

Papers Using SCHIF

In recent years, a method that might be viewed as an alternative to splines for assessing shape has been developed called shape-constrained health impact functions (SCHIF). The original paper describing this method appears to be Nasari et al. (2016). That paper contains illustrative examples of the method using data from the American Cancer Society (ACS) cohort and from the 1991 Canadian Community Health Environmental Cohort (CanCHEC91). The latter cohort was analyzed in Crouse et al. (2015), with the estimated shape illustrated in Figure 2 of these comments. Although Nasari et al. appears intended to be illustrative only, its SCHIF application to the CanCHEC91 appears to have reasonably well matched that of Crouse (2015).

[9] Shi et al. (2016); Lee et al. (2016); Di et al. (2017b).

One might infer that the SCHIF method would produce results little different than those from the more common spline-based methods. However, for the reasons described below, we are concerned that this may not be the case, and we feel that the SCHIF method of estimating shapes needs closer study and inspection before it should be relied upon for making policy judgments. It appears that the ISA authors may have already made that determination by not mentioning SCHIF at all. Should the lack of citations to SCHIF-based $PM_{2.5}$ papers turn out to be a mere oversight, however, we explain why such papers should not be given as much weight as spline-based methods until it has been explored and tested in more depth.

We have identified two Canadian papers that rely on SCHIF for estimating $PM_{2.5}$ C-R shapes for mortality: Pinault et al. (2017) and Weichenthal et al. (2017). In the former, the authors both developed a new CanCHEC cohort using 2001 data (CanCHEC01) and then developed "ensemble" estimates of C-R functions by likelihood function-weighted averaging of a family of pre-specified potential shapes (defined by the setting of multiple different parameters of a complex C-R formula that allows for the shape to vary away from the linear shape of a standard CPH model). The second paper also used the new CanCHEC01 cohort and used the SCHIF formula to estimate a C-R function for $PM_{2.5}$ in which the rate of increase in relative risk for increasing $PM_{2.5}$ exposures can vary depending on the level of oxidants in the ambient atmosphere.[10] They reported significant effect modification of the $PM_{2.5}$ C-R by oxidants. Indeed, when oxidant levels were below their top tertile, the standard CPH estimate of the $PM_{2.5}$ association was null, yet it was strongly significant when oxidant levels were in the top tertile.[11]

In both papers, when SCHIF was applied, the resulting estimates of best-fit shapes were strongly supralinear. In fact, these C-R results stand out as dramatically different from almost all of the literature that has been based on spline-based estimates. This can be seen in Figure 6 (at the end of this document), which has added the nonaccidental risk curves from these two papers to those in Figure 2 for all other Canadian nonaccidental risk shape estimates.[12] Before giving weight to these new results from a new estimation method, one ought to carefully consider the degree of incremental mortality risk that is being predicted between 0 and 5 $\mu g/m^3$: a 30% higher risk of nonaccidental death if exposed to 5 $\mu g/m^3$ as relative to that at 0 $\mu g/m^3$.[13] These two papers are the only ones in the evidence base using the CanCHEC01 cohort, so it is not possible to determine if these results might be attributable to the use of SCHIF or to some feature of this study's datasets. We also note that the only other C-R relationship that matches these results is another one by the same lead author, Pinault et al. (2016). Interestingly, that analysis has only the authorship in common, as it is based on a different Canadian cohort and used a more traditional spline-based shape estimation method.[14] Even if the results could be verified, one would be left to wonder whether there is something very unique about the $PM_{2.5}$ constituent mix that exists in Canada within that very low concentration range (which may also prevail in areas of Canada far from the U.S. border).

---

[10] Oxidant concentrations were estimated as a redox-weighted average of ambient ozone (average of 8-hour maximum values May to October and ambient NO_2 (annual average). The formula is $[(1.07*NO_2)+(2.075*O_3)]/3.145$.

[11] Figure 1 of Weichenthal et al. (2017).

[12] For Weichenthal et al., we present the curve estimated for an oxidant level of 37.6 ppb, which appears to be a level consistent with U.S. conditions (and found mainly along the U.S.-Canadian border inside Canada).

[13] SCHIF-based curves are not defined solely on their range of observations, as they have parametric definitions just like CPH. However, the minimum $PM_{2.5}$ exposure in this cohort is reported to be 0.01 $\mu g/m^3$ (Pinault et al., 2017, p. 410).

[14] We also note that Pinault is one of the three authors of Weichenthal et al., and all three of those authors are also co-authors of Pinault et al. (2017), albeit with many other co-authors. While overlapping co-authorship does not imply any issue with the credibility of these papers, we note that these papers should not be viewed as completely independent of each other for reasons beyond their common cohort and estimation method.

In conclusion, although we raise attention to the missing evidence on C-R shape in the ISA, we caution that these two papers are extremely different and that too many questions remain for explaining those differences to give weight to the supralinear nature of their results. More study is in order first, and if they are added to the ISA, we would recommend that these questions be clearly laid out.

Papers Using Subcategorization

A less sophisticated and generally less powerful method for exploring shape of C-Rs is to subcategorize the exposure observations into either quantiles or other subsets of the exposure observations. We note that a few of the papers cited in the ISA do use this method, and we have identified a couple of other such papers. Table 1 (on the next page) summarizes all the papers cited in the ISA and the others we have identified that use some form of subcategorization to estimate apparent shape. An interesting result is that there are 5 instances in which a subcategorization method was used in addition to directly estimating shape using smoothing methods. Of these, 2 seem to detect supralinearity with the subcategorization method, while their associated direct shape estimates indicated sublinearity.[15] Thus, one must conclude that subcategorization is not a reliable method. For this reason, we describe shape results from the subcategorization method as an "apparent" shape.

Papers with Shape Information for Other Endpoints

Our comments have focused on the two key mortality endpoints: nonaccidental and cardiovascular. We note that the ISA also discusses C-R shape with respect to diabetes/metabolic risk, and lung cancer. In the interests of completeness, we note two additional papers that we believe have relevant information on shape in these other mortality endpoint categories:

- Lim et al. (2018) – diabetes (linear)
- Deng et al. (2017) – mortality from liver cancer among those diagnosed already (sublinear)

[15] The two are the long-term C-R relationships in Di et al. (2017a) and in Shi et al. (2016).

Table 1. Summary of Papers Using Subcategorization to Explore Shape

Cited in ISA?	Paper	Mortality Endpoint	Form of subcategories	Result	Result if smoothing also used
Yes	Gan et al. (2011)	Cardiovascular	Quintiles	Same slope in all quintiles, but all were statistically insignificant (apparent linearity, if any effect at all)	No
Yes	Lee et al. (2016)	Acute all-cause	Low $PM_{2.5}$ subsets of exposure vs. full cohort	Higher CPH RR in low exposure conditions (possible supralinearity)	No
Yes	Di et al. (2017a)	Long-term all-cause	Subset of person-years with PM2.5< 12 µg/m^3 annual average and ozone < 50 ppb	Higher slope in subset (apparent supralinearity)	Yes – linear (slight sublinearity at lowest concentrations)
Yes	Di et al. (2017b)	Acute all-cause	Subset of days with PM2.5< 25 µg/m^3 or ozone < 60 ppb	Higher slope in subset (apparent supralinearity)	Yes – supralinear
Yes	Shi et al. (2016)	Acute all-cause	Subset of days <30 µg/m^3 vs. all days of data	Same slope in subset (apparent linearity)	Yes – slightly sublinear
		Long-term all-cause	Subset of person times <10 µg/m^3 annual average vs. all cohort	Higher slope in subset (apparent supralinearity)	Yes – sublinear
No	Deng et al. (2017)	Survival times for liver cancer	Categorized $PM_{2.5}$ into 6 levels	Increasing hazard ratios by category (apparent sublinearity)	Yes – sublinear
No	Schwartz et al. (2017)	Acute all-cause	Subset of days <30 µg/m^3 vs. all days of data	Slightly lower RR for the low-PM subset of data (apparent sublinearity)	No
No	Makar et al. (2017)	Long-term all-cause	Subset of person-years with PM2.5< 12 µg/m^3 annual average	Higher slope in subset, but neither estimate was statistically significant (apparent supralinearity)	No
No	Corrigan et al. (2018)	Long-term all-cause	Categorized regions by NAAQS attainment	Larger life expectancy gain in attainment areas (apparent supralinearity)	No

5. C-R Shapes Are Still Subject to Both Statistical and Model Uncertainty

Up to this point in these comments we have presented only the "best estimate" of the C-R shapes presented in each of the papers (i.e., in Figures 1 through 6). This emphasis on the "best estimate" shapes was necessary just to be able to show that a wide diversity of shape estimates presently exists, even if one limits oneself to "best estimates" of C-R shape. However, it is important to also realize that each one of those shape estimates is subject to statistical uncertainty due to the variance (or "noise") that is inherent in the data on which each of them was estimated. Information on such uncertainty is important to the question of whether the reported C-R relationship actually continues to exist down to the LML in each study – a question that is fundamental to the policy judgment that must be made regarding the level at which to set a NAAQS when the evidence of effect is primarily from epidemiological studies.[16]

The statistical uncertainty associated with each estimated C-R curve is most frequently summarized by confidence bounds (also presented as curves) around each curve. Figure 7 shows the confidence bounds around the C-R curve from Chen et al. (2016). The solid curve in Figure 7 is the "best estimate" of the shape of the C-R relationship implied by the dataset that Chen et al. used and is the C-R shape estimate that appears as the red curves in Figures 2 and 6. Figure 7 also reveals that the C-R shape implied by that solid curve is far from well-defined: the dotted curves that surround the solid curve represent the 95% confidence interval around that shape and can be thought of as representing the statistical error on the estimated slope of the solid curve *at each point along that curve* from the lowest to the highest measured level in the dataset used to estimate the curve.

One way to interpret the two dotted curves in Figure 7 is that their slopes *at any given $PM_{2.5}$ level* represent the upper and lower ends of the 95-percent statistical uncertainty range around the best estimate of the slope of the C-R at that $PM_{2.5}$ exposure level. These values frame the best estimate of the slope of the C-R relationship at that exposure level, which is defined by the slope of the *solid* curve at that same $PM_{2.5}$ level. For example, in the exposure zone near the LML in Figure 7 the solid curve is nearly flat (suggesting very little incremental risk for the first few increments of exposure above the LML), and the confidence intervals on that slope range from negative (the slope of the upper dotted curve near the LML) to positive (the slope of the lower dotted curve). Thus, just above the LML, the estimated C-R relationship has a very small positive slope with a confidence interval from quite negative to quite positive. This is equivalent to saying that the slope *at that* point is not statistically significant or cannot be said to be different from zero. A zero slope is equivalent to there being no C-R relationship at that level of exposure. Thus, for this particular study, although a "best estimate" shape (solid curve) is reported down to the study's LML, the "existence" of such a curve does not mean this study provides support for the hypothesis that the C-R relationship continues to exist down to the LML.

The example considers the confidence interval on the slope at or just above the LML for the Chen et al. (2016) study. The same logic can be applied at any exposure level within the observed range. That is, using C-R curves allows the estimate of relative risk per unit of incremental $PM_{2.5}$ exposure to vary with the $PM_{2.5}$ level, in contrast to the result from a standard CPH model in which only a single relative risk estimate is attributed to the entire exposure range. The curves that represent the 95-percent bounds around a given curve estimate similarly allow the confidence range on the C-R's slope to also vary with the $PM_{2.5}$ level. Statistically significant evidence of non-zero risk at a particular exposure depends on the confidence range on C-R slope at that exposure level rather than on whether the best estimate of the slope (i.e., the solid curve's slope) is positive.

[16] For a discussion of the importance of uncertainty in the continued existence of the C-R relationship in setting the $PM_{2.5}$ NAAQS, see Smith (2018).

The same observations apply to the other papers we have examined in these comments: each study reported here has its own $PM_{2.5}$-varying confidence intervals to determine where its slope estimate is statistically-significantly positive. Some studies reflect greater uncertainty than others toward their respective LMLs, just as they also vary in their best estimate of C-R shape. These study-specific confidence bounds, however, reflect only the statistical variance component of uncertainty in the true C-R relationship. Model uncertainty is an important additional consideration when evaluating the strength of evidence for the continued existence of a $PM_{2.5}$ C-R relationship at relatively low $PM_{2.5}$ concentrations.

Model uncertainty arises because the functional form of the true C-R relationship is unknown. Thus, each of the papers we discuss here had to select one (or a set) of plausible models of this relationship. The curves presented in Figures 1 through 6 depend in part on these modeling assumptions. For instance, those papers that modeled the curves with splines had to select the number of knots that define the spline, as well as the location of each knot along the range of $PM_{2.5}$. Different choices of the number or location of these knots would have led to different shapes. Similarly, the C-R shapes in those papers that use the SCHIF method may be defined in part by parameter values selected by the researcher for their "family" of curves. Again, different choices of these researcher-defined parameters will lead to different curves. Many of these papers identify the best-fitting model from among their candidates through a comparison of statistical goodness-of-fit measures, but this does not address the model uncertainty that arises from multiple plausible candidate models.

Thus, evaluating model uncertainty also requires inter-study comparisons. To a partial degree, the inter-study comparisons of the solid curves provided in Figures 1 through 6 indicate a substantial degree of model uncertainty, possibly exceeding their individual statistical uncertainties. That is, those inter-study comparisons based solely on the "best estimates" of each study's shape indicate a wide range of uncertainty in slopes, with wider uncertainty at the lower concentration levels. However, a more comprehensive evaluation of both model and statistical uncertainty is warranted to fully address the issue of where confidence in the C-R relationship's continuation becomes unacceptably low to warrant a NAAQS.

6. Conclusions

The following is a brief synopsis of the key points in these comments, which have focused solely on the ISA's discussions of evidence on the shape of the C-R relationship:

- There are more examples in the literature of shape estimates than in earlier reviews.
- Those estimates of shape are highly varied, ranging from sublinear to supralinear.
- Although there has been much recent discussion of emerging evidence of a supralinear C-R relationship, the ISA is correct to recognize that such evidence is counterbalanced by less widely discussed offsetting examples in which the estimated shapes are sublinear.
- The confidence intervals around the reported shape estimates further erode the view that there is strong evidence on shapes, particularly as concentrations decline toward the LMLs in these studies.
- Understanding the evidence in favor of continued existence of a C-R relationship at relatively low exposures will require a synthesis of both model uncertainty and statistical uncertainty that the ISA has not yet conducted.

References

Chen, H; Burnett, RT; Copes, R; Kwong, JC; Villeneuve, PJ; Goldberg, MS; Brook, RD; van Donkelaar, A; Jerrett, M; Martin, RV; Brook, JR; Kopp, A; Tu, JV. (2016). Ambient fine particulate matter and mortality among survivors of myocardial infarction: population-based cohort study. Environ Health Perspect 124: 1421-1428.

Corrigan, AE; Becker, MM; Neas, LM; Cascio, WE; Rappold, AG. (2018). Fine particulate matters: The impact of air quality standards on cardiovascular mortality. Environ Res 161: 364-369.

Crouse, DL; Peters, PA; van Donkelaar, A; Goldberg, MS; Villeneuve, PJ; Brion, O; Khan, S; Atari, DO; Jerrett, M; Pope, CA; Brauer, M; Brook, JR; Martin, RV; Stieb, D; Burnett, RT. (2012). Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. Environ Health Perspect 120: 708-714.

Crouse, DL; Peters, PA; Hystad, P; Brook, JR; van Donkelaar, A; Martin, RV; Villeneuve, PJ; Jerrett, M; Goldberg, MS; Pope, CA; Brauer, M; Brook, RD; Robichaud, A; Menard, R; Burnett, RT. (2015). Ambient PM 2.5, O 3, and NO 2 exposures and associations with mortality over 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect 123: 1180-1186.

Deng, H; Eckel, SP; Liu, L; Lurmann, FW; Cockburn, MG; Gilliland, FD. (2017). Particulate matter air pollution and liver cancer survival. Int J Cancer 141: 744-749.

Di, Q; Wang, Y; Zanobetti, A; Wang, Y; Koutrakis, P; Choirat, C; Dominici, F; Schwartz, JD. (2017a). Air pollution and mortality in the Medicare population. N Engl J Med 376: 2513-2522.

Di, Q; Dai, L; Wang, Y; Zanobetti, A; Choirat, C; Schwartz, JD; Dominici, F. (2017b). Association of short-term exposure to air pollution with mortality in older adults. JAMA 318: 2446-2456.

Gan, W; Koehoorn, M; Davies, H; Demers, P; Tamburic, L; Brauer, M. (2011). Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. Environ Health Perspect 119: 501-507.

Hart, JE; Liao, X; Hong, B; Puett, RC; Yanosky, JD; Suh, H; Kioumourtzoglou, MA; Spiegelman, D; Laden, F. (2015). The association of long-term exposure to PM2.5 on all-cause mortality in the Nurses' Health Study and the impact of measurement-error correction. Environ Health 14: 38.

Jerrett, M; Turner, MC; Beckerman, BS; Pope, CA; van Donkelaar, A; Martin, RV; Serre, M; Crouse, D; Gapstur, SM; Krewski, D; Diver, WR; Coogan, PF; Thurston, GD; Burnett, RT. (2017). Comparing the health effects of ambient particulate matter estimated using ground-based versus remote sensing exposure estimates. Environ Health Perspect 125: 552-559.

Lee, M; Koutrakis, P; Coull, B; Kloog, I; Schwartz, J. (2016). Acute effect of fine particulate matter on mortality in three southeastern states from 2007-2011. J Expo Sci Environ Epidemiol 26: 173-179.

Lepeule, J; Laden, F; Dockery, D; Schwartz, J. (2012). Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. Environ Health Perspect 120: 965-970.

Lim, CC; Hayes, RB; Ahn, J; Shao, Y; Silverman, DT; Jones, RR; Garcia, C; Thurston, GD. (2018). Association between long-term exposure to ambient air pollution and diabetes mortality in the US. Environ Res 165: 330-336.

Makar, M; Antonelli, J; Di, Q; Cutler, D; Schwartz, J; Dominici, F. (2017). Estimating the Causal Effect of Low Levels of Fine Particulate Matter on Hospitalization. Epidemiology 28: 627-634.

Nasari, MM; Szyszkowicz, M; Hong, C; Crouse, D; Turner, MC; Jerrett, M; Pope, CA; Hubbell, B; Fann, N; Cohen, A; Gapstur, SM; Diver, WR; Stieb, D; Forouzanfar, MH; Kim, S; Olives, C; Krewski, D; Burnett, RT. (2016). A class of non-linear exposure-response models suitable for health impact assessment applicable to large cohort studies of ambient air pollution. Air Qual Atmos Health 9: 961-972.

Pinault, L; Tjepkema, M; Crouse, DL; Weichenthal, S; van Donkelaar, A; Martin, RV; Brauer, M; Chen, H; Burnett, RT. (2016). Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. Environ Health 15: Article #18.

Pinault, LL; Weichenthal, S; Crouse, DL; Brauer, M; Erickson, A; Donkelaar, AV; Martin, RV; Hystad, P; Chen, H; Finès, P; Brook, JR; Tjepkema, M; Burnett, RT. (2017). Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. Environ Res 159: 406-415.

Schwartz, J; Bind, MA; Koutrakis, P. (2017). Estimating Causal Effects of Local Air Pollution on Daily Deaths: Effect of Low Levels. Environ Health Perspect 125: 23-29.

Shi, L; Zanobetti, A; Kloog, I; Coull, BA; Koutrakis, P; Melly, SJ; Schwartz, JD. (2016). Low-concentration PM2.5 and mortality: estimating acute and chronic effects in a population-based study. Environ Health Perspect 124: 46-52.

Smith, AE. (2018). Setting air quality standards for $PM_{2.5}$: A role for subjective uncertainty in NAAQS quantitative risk assessments? Risk Analysis 38: 2318-2339.

Thurston, GD; Ahn, J; Cromar, KR; Shao, Y; Reynolds, HR; Jerrett, M; Lim, CC; Shanley, R; Park, Y; Hayes, RB. (2016). Ambient particulate matter air pollution exposure and mortality in the NIH-AARP Diet and Health Cohort. Environ Health Perspect 124: 484-490.

Villeneuve, PJ; Weichenthal, SA; Crouse, D; Miller, AB; To, T; Martin, RV; van Donkelaar, A; Wall, C; Burnett, RT. (2015). Long-term exposure to fine particulate matter air pollution and mortality among Canadian women. Epidemiology 26: 536-545.

Weichenthal, S; Pinault, LL; Burnett, RT. (2017). Impact of Oxidant Gases on the Relationship between Outdoor Fine Particulate Air Pollution and Nonaccidental, Cardiovascular, and Respiratory Mortality. Sci Rep 7: 16401.

Weichenthal, S; Villeneuve, PJ; Burnett, RT; van Donkelaar, A; Martin, RV; Jones, RR; Dellavalle, CT; Sandler, DP; Ward, MH; Hoppin, JA. (2014). Long-term exposure to fine particulate matter: association with nonaccidental and cardiovascular mortality in the agricultural health study cohort. Environ Health Perspect 122: 609-615.

Figure 1. U.S. Long-term Nonaccidental C-R Shape Estimates for 4 of the 5 Papers Cited in ISA.
(Hart et al. (2015) not included: does not provide any of its non-linear estimates, just states they were not significantly different from linear.)

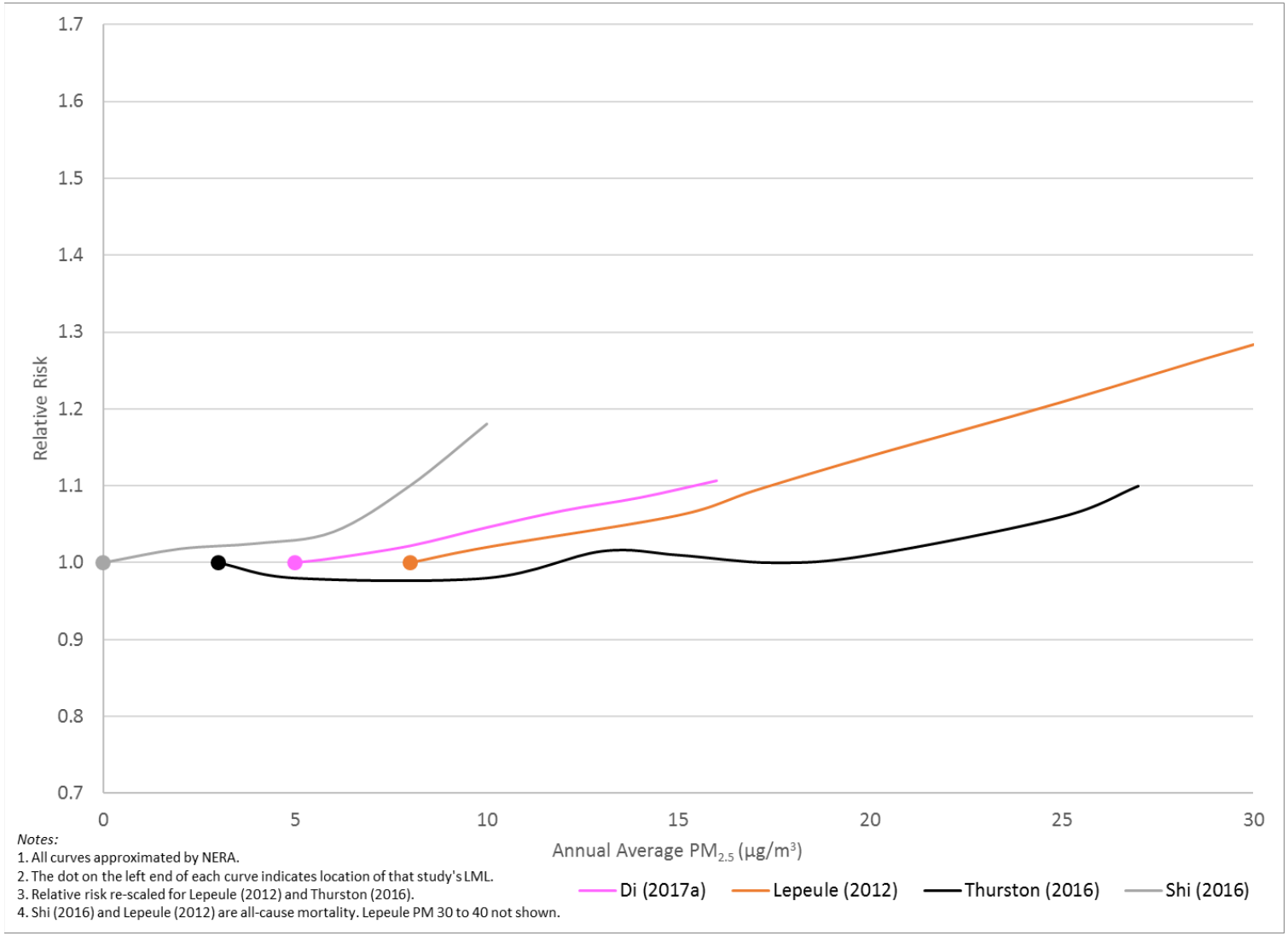
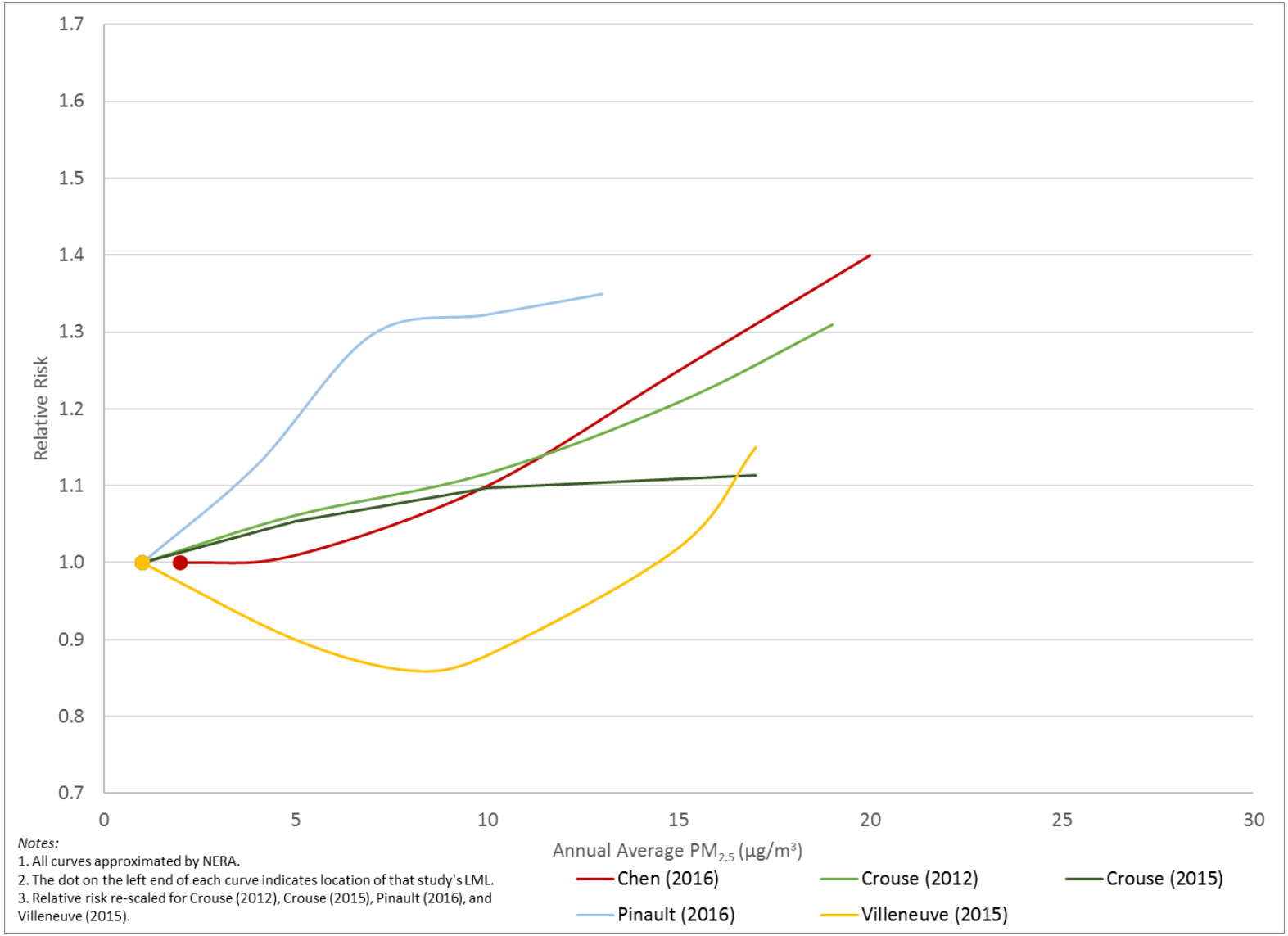
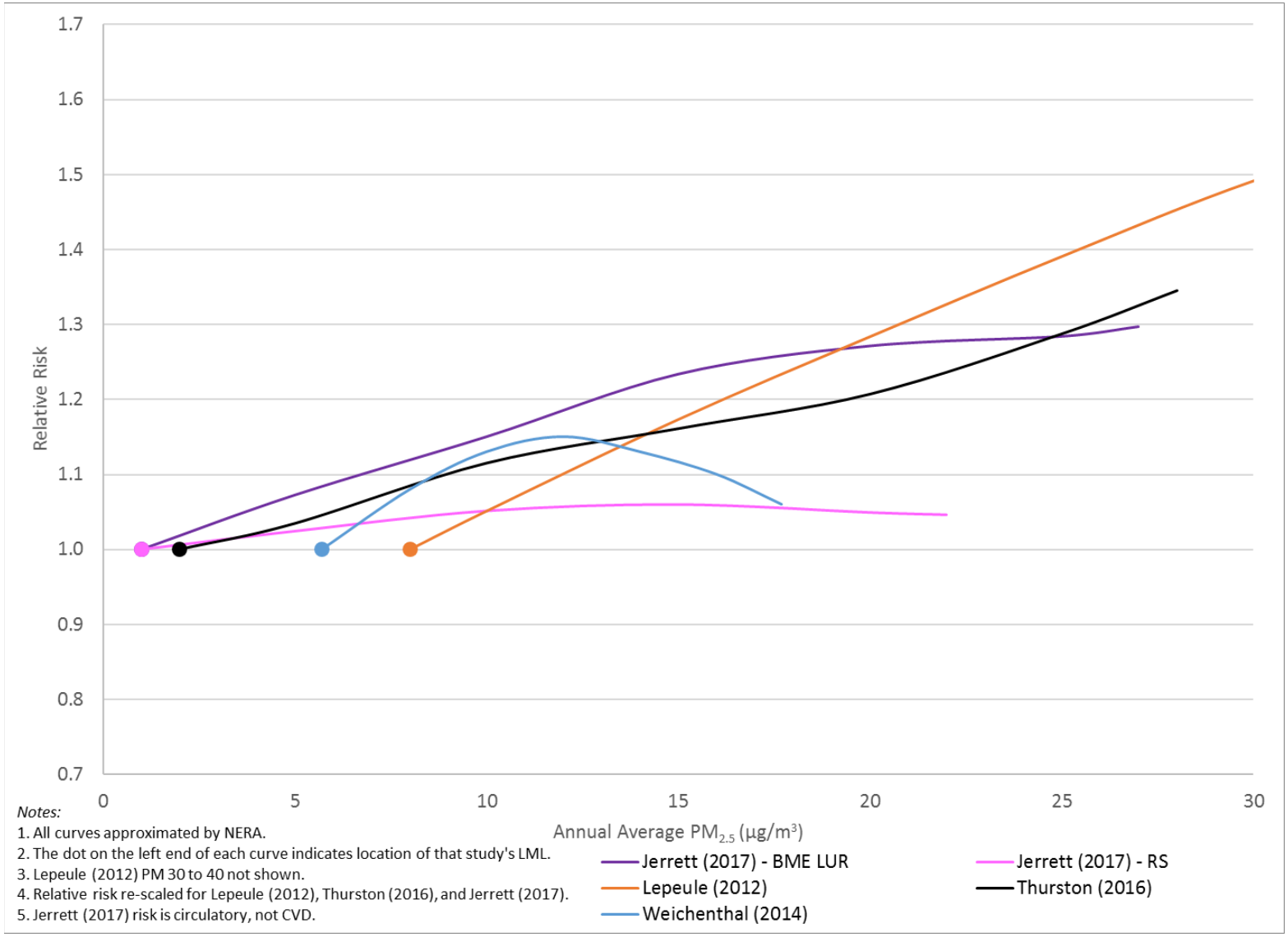


Figure 2. Canadian Long-term Nonaccidental C-R Shape Estimates for 5 Papers Cited in ISA



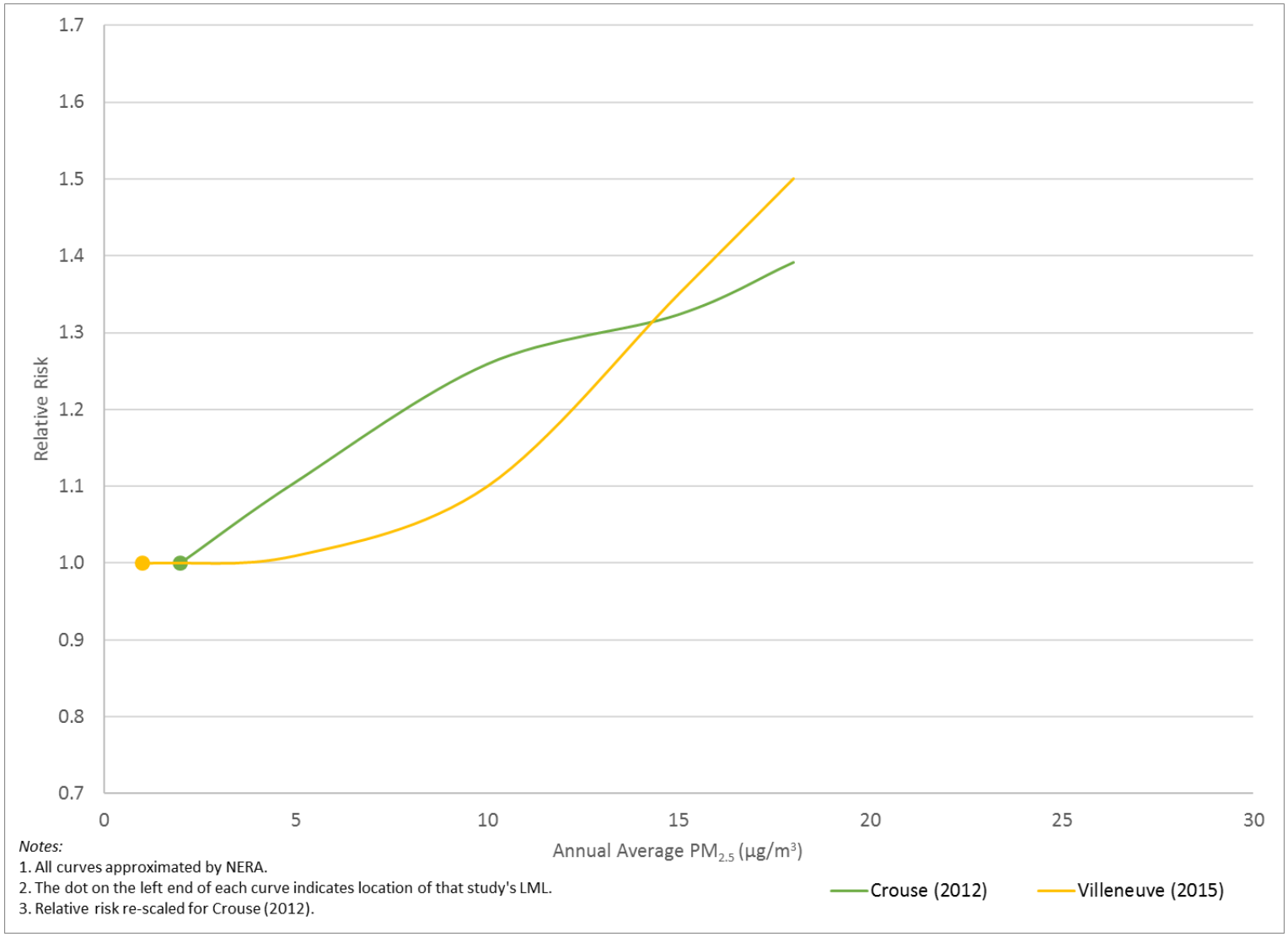
Notes:
1. All curves approximated by NERA.
2. The dot on the left end of each curve indicates location of that study's LML.
3. Relative risk re-scaled for Crouse (2012), Crouse (2015), Pinault (2016), and Villeneuve (2015).

Figure 3. U.S. Long-term Cardiovascular C-R Shape Estimates for 4 Papers Cited in ISA



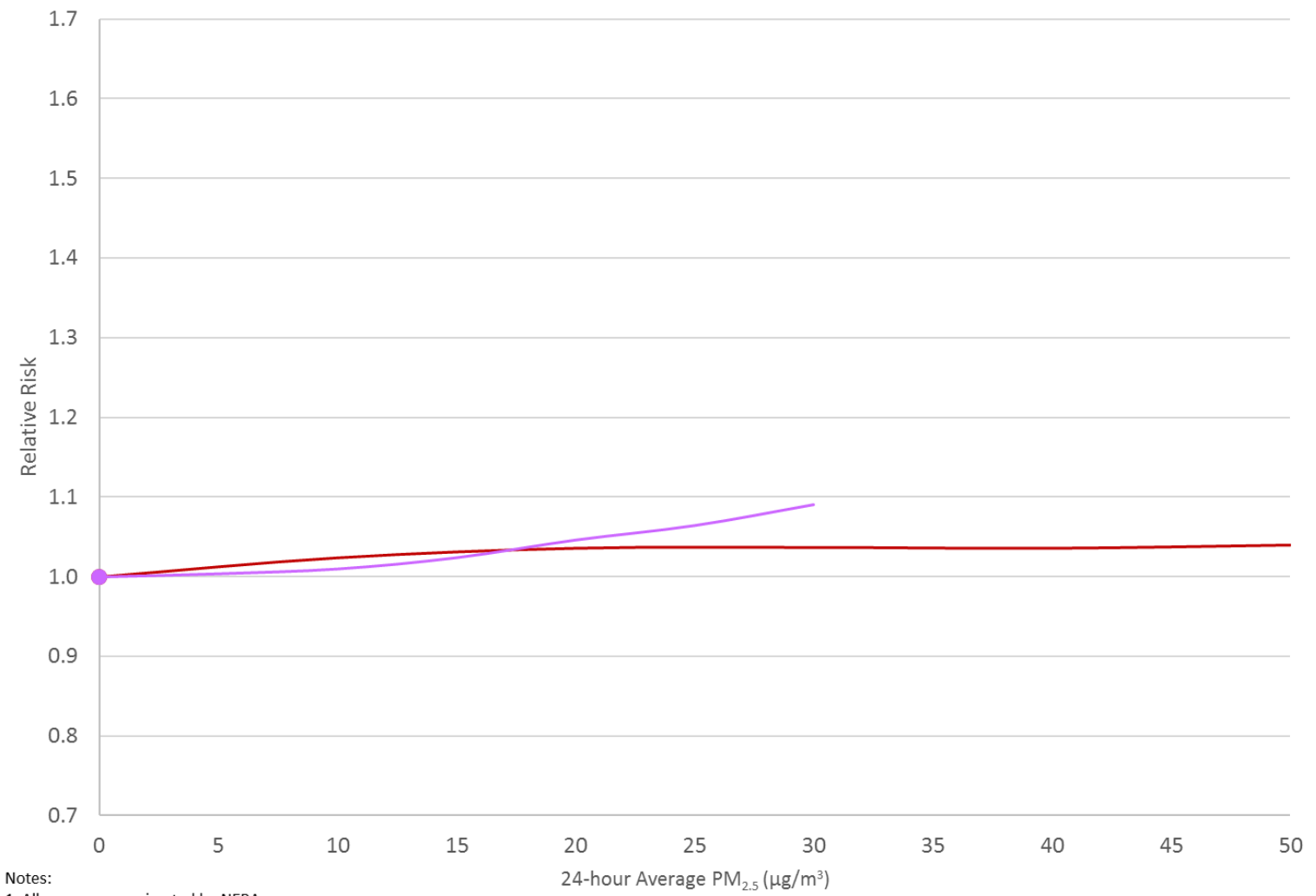
Notes:
1. All curves approximated by NERA.
2. The dot on the left end of each curve indicates location of that study's LML.
3. Lepeule (2012) PM 30 to 40 not shown.
4. Relative risk re-scaled for Lepeule (2012), Thurston (2016), and Jerrett (2017).
5. Jerrett (2017) risk is circulatory, not CVD.

Figure 4. Canadian Long-term Cardiovascular C-R Shape Estimates for 2 of 3 Papers Cited in ISA
(Gan et al. (2011) not included: used CPH by quintile rather than smoothing; no quintile shows statistically significant $PM_{2.5}$ relative risk.)



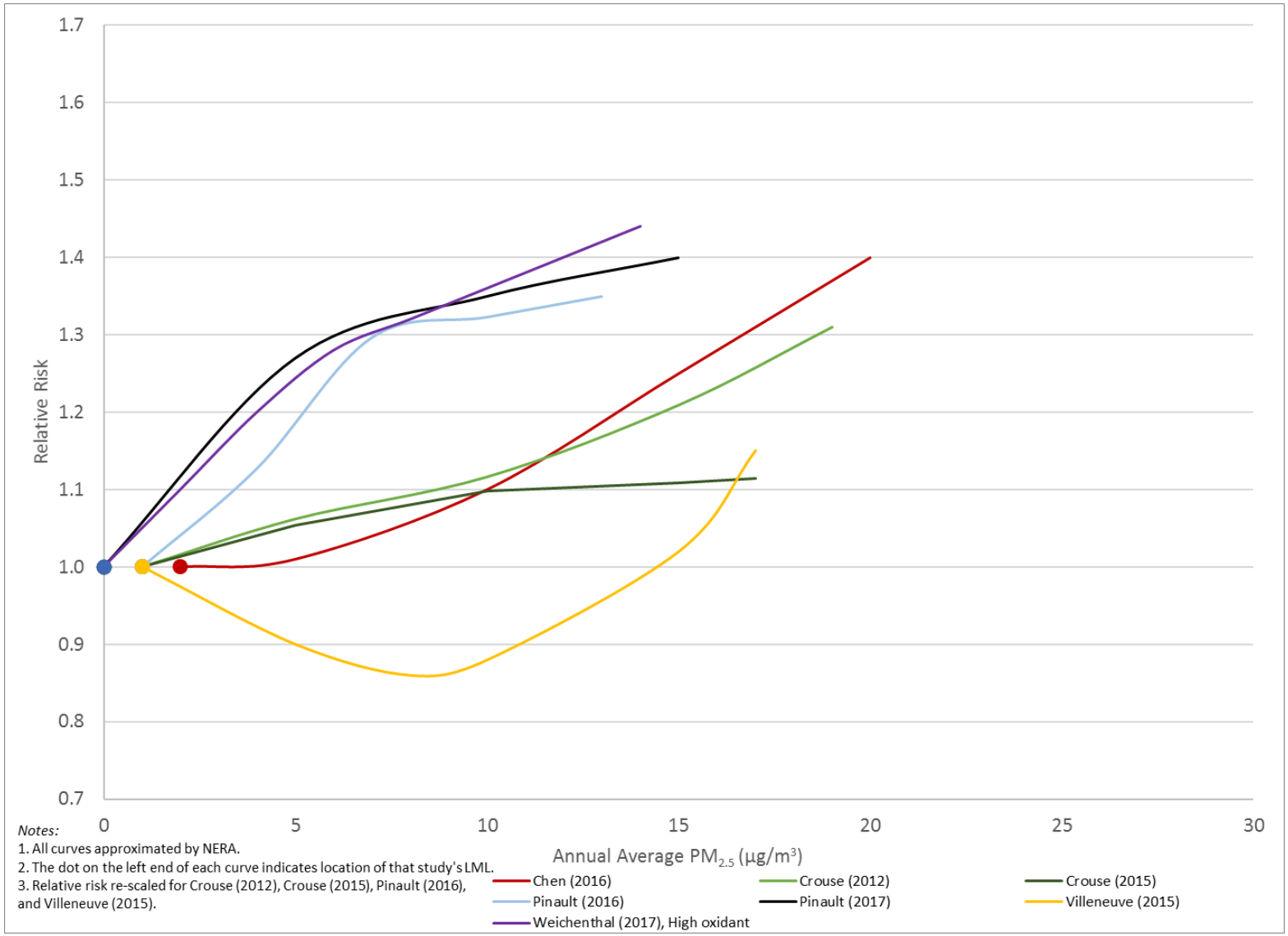
Notes:
1. All curves approximated by NERA.
2. The dot on the left end of each curve indicates location of that study's LML.
3. Relative risk re-scaled for Crouse (2012).

Figure 5. U.S. Short-term All-Cause C-R Shape Estimates for 2 of 3 Papers Cited in ISA
(Lee et al. (2016) not included: it compares CPH slopes estimated over all PM and only on days below current NAAQS rather than estimating shape directly; its results suggested supralinearity. *Note that the shape from Shi et al. is estimated on the subset of days <30 μg/m³*.)



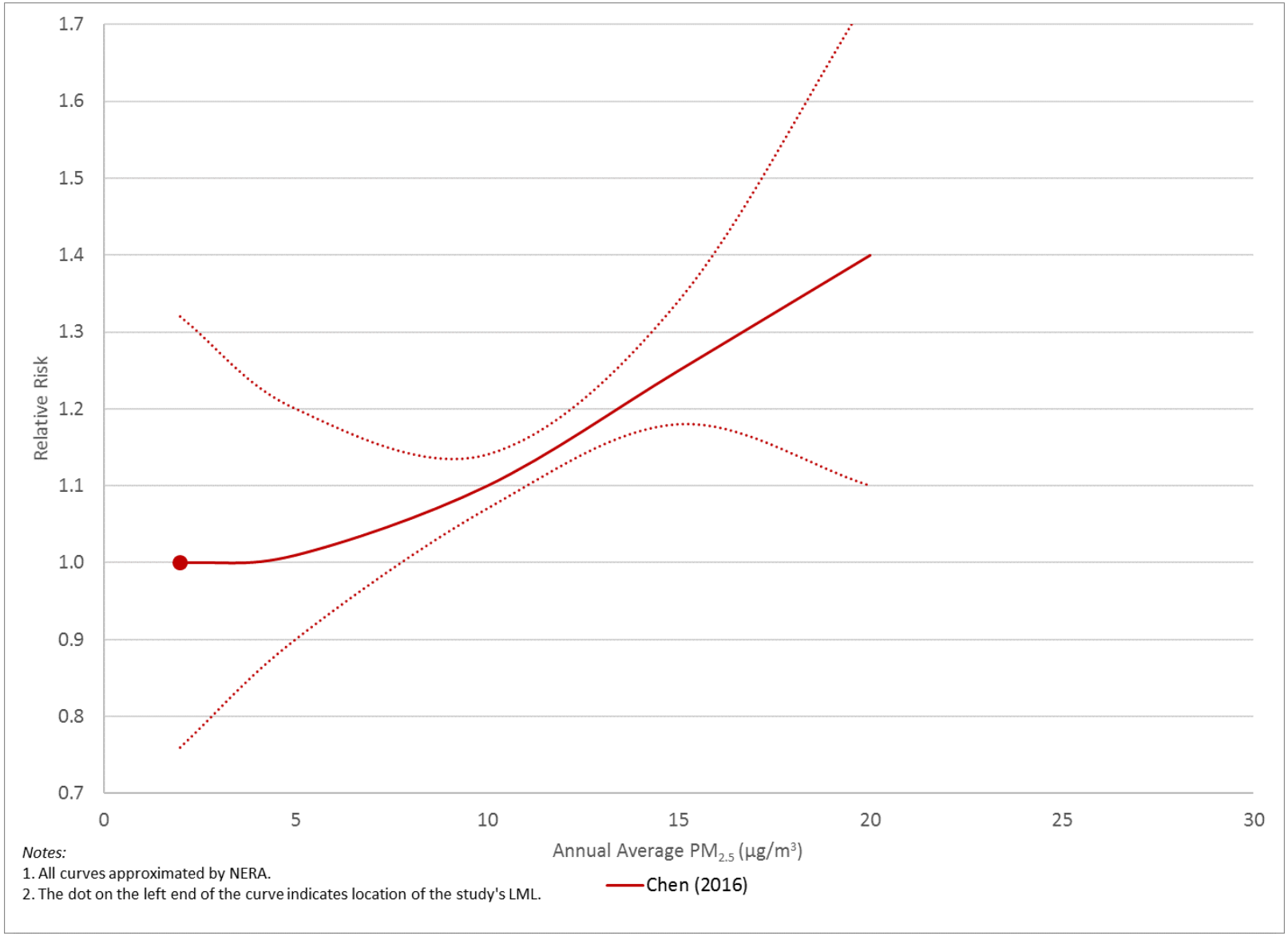
Notes:
1. All curves approximated by NERA.
2. The dot on the left end of each curve indicates the location of that study's LML.
3. Shi (2016) is only for daily concentrations of less than 30 μg/m³.

Figure 6. Canadian Long-term Nonaccidental C-R Shape Estimates for 5 Papers Cited in ISA, Plus C-R Shapes from 2 SCHIF-Based Estimations Not Cited in ISA (i.e., Pinault et al., 2017 and Weichenthal et al., 2017)



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 Crouse (2012), Crouse (2015), Pinault (2016), and Villeneuve (2015).

Figure 7. Example of Confidence Intervals That Surround Each C-R Curve from Chen et al. (2016)



Notes:
1. All curves approximated by NERA.
2. The dot on the left end of the curve indicates location of the study's LML.