

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON D.C. 20460



OFFICE OF THE ADMINISTRATOR  
SCIENCE ADVISORY BOARD

EPA-SAB-20-xxx

The Honorable Andrew Wheeler  
Administrator  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, N.W.  
Washington, D.C. 20460

Subject: Transmittal of the Science Advisory Board’s Consideration of the Scientific and Technical Basis of EPA’s Proposed Rule titled “Increasing Consistency and Transparency in Considering Benefits and Costs in the Clean Air Act Rulemaking Process.”

Dear Administrator Wheeler:

As part of its statutory duties, the EPA Science Advisory Board (SAB) may provide advice and comments on the scientific and technical basis of certain planned EPA actions pursuant to the Environmental Research, Development, and Demonstration Authorization Act of 1978 (ERDDAA) which requires the EPA to make available to the SAB proposed criteria documents, standards, limitations, or regulations, together with relevant scientific and technical information on which the proposed action is based. On the basis of this information, the SAB may provide advice and comments. Thus, the SAB is submitting the attached report on EPA’s Proposed Rule titled “Increasing Consistency and Transparency in Considering Benefits and Costs in the Clean Air Act Rulemaking Process” published in the Federal Register on June 11, 2020 (85 FR 35612-35627). In developing this report, the SAB followed the engagement process for review of regulatory actions outlined in your memo of February 25, 2020.

The Proposed Rule establishes procedural requirements governing the development and presentation of benefit-cost analyses (BCA) for significant rulemakings conducted under the Clean Air Act (CAA) to ensure consistency and transparency. The Proposed Rule requires that EPA: (1) prepare a BCA for all significant CAA proposed and final regulations; (2) adhere to best practices for the development of the BCA; and (3) provide a transparent presentation of the BCA results in the rule preamble.

The SAB met by videoconference on August 11, 2020 and September 15, 2020 and reviewed the scientific and technical basis of the Proposed Rule. The SAB’s advice and comments are provided in the enclosed report and summarized below.

**Science Advisory Board (SAB) Draft Report (09/08/20) – Do Not Cite or Quote.**  
**This draft has not been reviewed or approved by the chartered SAB and does not represent EPA policy**

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The SAB’s major comments and recommendations are as follows:

- EPA should clarify and strengthen the estimation of benefits in the proposed rule by incorporating systematic review approaches, better defining causality, and including effects for which causal or likely causal relationships may be less certain.
- EPA should clarify and strengthen recommendations on the selection of health endpoints, especially with regard to the selection of concentration response functions.
- EPA should clarify and strengthen the requirements for uncertainty analysis in the proposed rule by better aligning the rule language with current best practices, better incorporating low probability, high-consequence hazards, and clearly noting when unquantified benefits or costs could be significant.

The SAB appreciates the opportunity to provide the EPA with advice and comment on the Proposed Rule. We look forward to receiving the Agency’s response.

Sincerely,

Dr. Michael Honeycutt, Chair  
Science Advisory Board

Enclosure

**NOTICE**

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4 This report has been written as part of the activities of the EPA Science Advisory Board, a public  
5 advisory committee providing extramural scientific information and advice to the Administrator and  
6 other officials of the Environmental Protection Agency. The Board is structured to provide balanced,  
7 expert assessment of scientific matters related to problems facing the Agency. This report has not been  
8 reviewed for approval by the Agency and, hence, the contents of this report do not represent the views  
9 and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of  
10 the Federal government, nor does mention of trade names or commercial products constitute a  
11 recommendation for use. Reports of the EPA Science Advisory Board are posted on the EPA website at  
12 <http://www.epa.gov/sab>.  
13

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Science Advisory Board (SAB) Report on EPA’s Proposed Rule  
“Increasing Consistency and Transparency in Considering Benefits and Costs in the Clean Air  
Act Rulemaking Process”

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**ACRONYMS AND ABBREVIATIONS**

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5	BCA	Benefit-Cost Analysis
6	CAA	Clean Air Act
7	CCS	Congestion Charging Scheme
8	C-R	Concentration-Response
9	EO	Executive Order
10	HEI	Health Effects Institute
11	IRIS	Integrated Risk Information System
12	ISA	Integrated Science Assessment
13	LEZ	Low Emissions Zone
14	MOA	Mode of Action
15	NAAQS	National Ambient Air Quality Standards
16	NASEM	National Academy of Sciences, Engineering and Medicine
17	OMB	Office of Management and Budget
18	SAB	Science Advisory Board
19	TSCA	Toxic Substances Control Act
20	U.S. EPA	U.S. Environmental Protection Agency
21	WoE	Weight of Evidence
22		

1 **1. INTRODUCTION**

2  
3 The EPA’s Proposed Rule titled “Increasing Consistency and Transparency in Considering Benefits  
4 and Costs in the Clean Air Act Rulemaking Process” was published on June 11, 2020 in the Federal  
5 Register (Environmental Protection Agency, 2020). The Proposed Rule would establish procedural  
6 requirements governing the development and presentation of benefit-cost analyses (BCA) for significant  
7 rulemakings promulgated under the Clean Air Act (CAA). The SAB is offering comments on the extent  
8 to which the provisions in the Proposed Rule are consistent with best available scientific information  
9 and in accordance with best practices from the economic, engineering, physical, and biological sciences.

10  
11 The Proposed Rule establishes procedural requirements governing the development and presentation of  
12 benefit-cost analyses (BCA) for significant rulemakings conducted under the Clean Air Act (CAA) to  
13 ensure consistency and transparency. The Proposed Rule requires that EPA: (1) prepare a BCA for all  
14 significant CAA proposed and final regulations; (2) adhere to best practices for the development of the  
15 BCA; and (3) provide a transparent presentation of the BCA results in the rule preamble.

16  
17 In developing this report, the SAB followed the engagement process for review of regulatory actions  
18 outlined in Administrator Wheeler’s memo of February 25, 2020 (Wheeler, 2020). The SAB met by  
19 videoconference on August 11, 2020 and September 15, 2020 and reviewed the scientific and technical  
20 basis of the Proposed Rule. Oral and written public comments were considered throughout the advisory  
21 process. The SAB’s advice and comments follow below, organized by topics that arose from the SAB’s  
22 deliberations.

23  
24 In developing this report, the SAB kept in mind the Proposed Rule sought to codify practices outlined in  
25 existing peer reviewed guidance documents, including the EPA’s *Guidelines for Preparing Economic*  
26 *Analyses* (Environmental Protection Agency, 2010, Updated 2014). At the time of this writing, the  
27 *Guidelines* are undergoing a periodic update and the SAB Economic Guidelines Review Panel (SAB-  
28 EGRP) is reviewing the revisions contained in this update. Hence, the SAB sought to limit its review to  
29 requirements in the Proposed Rule that would not be addressed by the SAB-EGRP. Further SAB advice  
30 will be available with the completion of the SAB-EGRP’s report and its approval by the chartered SAB.

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## 2. SAB ADVICE AND COMMENTS ON THE PROPOSED RULE

### 2.1 Definitions

Section 83.1 of the Proposed Rule provides definitions of terms used in regulatory assessments. In the text below, the SAB provides some suggestions for improvement in the definitions. The first sentence in the revised text, as indicated in the footnote, is adapted from OMB Circular A-4. The second sentence explains the BCA should use opportunity costs (as opposed, for example, to accounting costs) and that benefits should be derived from willingness-to-pay estimates from domestic individuals (as opposed to international interests). The third sentence directly references what is in the current proposed rule draft.

- Benefit-Cost Analysis – The SAB recommends revising the definition of Benefit-Cost analysis in the proposed rule to clearly state that Benefit-cost analysis (BCA) analysis provides decision makers with a clear indication of the most efficient alternative, that is, the alternative that generates the largest net benefits (benefits minus costs) to society (ignoring distributional effects) (Office of Management and Budget, 2003). The definition should indicate that costs should be opportunity costs and benefits represent the willingness-to-pay for a policy outcome valued by United States individuals. The definition should also indicate that Benefit-Cost analysis addresses the question of whether the benefits for those who gain from the action are sufficient to, in principle, compensate those burdened such that everyone would be as well off as before the policy.
- Regulatory options – In this section, the current text advises economists to provide regulatory options that are both more and less stringent in addition to the option currently being considered for implementation. However, for benefit-cost analysis, as opposed to cost-effectiveness analysis, the regulatory options should only help to solve a problem, not accomplish a goal or objective. For example, a less stringent option might accomplish less but at lower cost. Therefore, the SAB recommends that the following parts of the definition of regulatory options be revised as indicated below:

“(2) From “A more stringent option which accomplishes the stated objectives of the Clean Air Act...” to “A more stringent option which *contributes to* the stated objectives of the Clean Air Act and that achieves additional benefits (and presumably costs more) beyond those realized by the proposed or finalized option; and”

“(3) from “A less stringent option which accomplishes the stated objectives of the Clean Air Act...” to “A less stringent option which *contributes to* the stated objectives of the Clean Air Act and that costs less (and presumably generates fewer benefits) than the proposed or finalized option.”

1    **2.2 Estimating Benefits**  
2

3    Section 83.3(a)(7) establishes requirements for the selection of benefit endpoints. In the text below, the  
4    SAB is offering its comments on the requirement that the Agency must select endpoints for which the  
5    scientific evidence indicates there is a clear causal or likely causal relationship between pollutant  
6    exposure and effect. The SAB is also offering recommendations for how to establish criteria for a  
7    weight of evidence determination on causality that would be appropriate to apply to all benefit  
8    endpoints.  
9

10   Several scientific issues are raised by the text of this section including: (1) whether benefits analyses for  
11   effects should be limited to those described as having a clear or likely causal relationship, and (2) what  
12   best practices can and should be applied to evaluate causality.

13       **2.2.1 Benefits analyses for effects that are clearly causal or likely causal**

14   It is essential for analyses to characterize health effects for which the science indicates the greatest  
15   likelihood that changes in exposure would provide positive benefits. The focus on clearly causal or  
16   likely causal relationships provides a useful analysis. If feasible, inclusion in the benefits analyses of  
17   effects for which the relationship may be less certain (e.g., possibly causal), but the impact would be  
18   substantial, could provide a more complete perspective accounting for uncertainties (McGartland, et al.,  
19   2017). Modification of the language in Section 82(a)(7) should allow such analyses, while the current  
20   language appears to exclude them.  
21

22   It remains unclear what specific criteria the Agency will use to determine causality. The Agency should  
23   transparently include in the rule, or reference, relevant guidance which provides clear definitions for  
24   “causal” and “likely causal” based on current best Agency practices. The Agency should also explain  
25   what types of scientific evidence are needed to justify a “causal” and “likely causal” determination (i.e.  
26   epidemiology, animal toxicology data, and mechanistic biology results should be considered). For  
27   example, the Agency has clear definitions that it uses in the development of its Integrated Science  
28   Assessment (Environmental Protection Agency, 2015). Additionally, the Agency should make clear the  
29   distinction between association vs. causation given that most epidemiological studies are by nature  
30   observational rather than experimental and thus there could be several potential reasons for an observed  
31   association that need to be evaluated before an inference can be made to support a cause-effect  
32   relationship.  
33

34   While cancer effects and a range of endpoints in Integrated Science Assessments (ISAs) are routinely  
35   characterized for their likelihood in humans, this is not generally done for many noncancer health effects  
36   for chemicals not assessed with ISAs. Analyses for these chemicals and endpoints have been described  
37   to permit characterization of the health risks arising from them (Clewel, HJ and Crump, KS, 2005).  
38   Including these endpoints would strengthen the benefits analyses.

39       **2.2.2 Systematic Review Framework**  
40

41   One approach for determining if there is a clearly causal or likely causal relationship is systematic  
42   review. A systematic review is a structured process of identifying, evaluating, and integrating evidence  
43   for the question under evaluation. Careful specification of the question to be addressed is essential to the  
44   utility of the systematic review. Prior to the start of the review, a protocol is written to describe the

1 methodology for searching for studies, determining if each study meets a predefined formulation  
2 defining the Population studied, the Exposure considered, the Comparator, and the Outcome (PECO).  
3 Criteria are determined prior to conducting the analysis for consistent evaluation of studies and an a  
4 priori framework for synthesizing and integrating studies to determine the strength of the evidence.  
5 When done correctly, the systematic review process increases transparency and reduces bias in decision  
6 making.

7  
8 EPA has developed a method for systematic reviews within their Integrated Risk Information System  
9 (IRIS) program. That approach has been reviewed favorably by the National Academy of Sciences,  
10 considering both the overall process (National Academy of Sciences, Engineering and Medicine, 2018),  
11 and when considering specific examples (National Academies of Sciences, Engineering and Medicine,  
12 2019). That process should be a model for this regulation. Additionally, if a systematic review has  
13 already been conducted for a specific pollutant and health endpoint, EPA may be able to be use it  
14 directly. The EPA may want to set standards for acceptable systematic reviews, such as those conducted  
15 by independent agencies that follow an approach similar to that followed in the IRIS program.

16  
17 For the Toxic Substances Control Act (TSCA), EPA has adopted the definition - “Weight of the  
18 scientific evidence means a systematic review method, applied in a manner suited to the nature of the  
19 evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently,  
20 and consistently identify and evaluate each stream of evidence, including strengths, limitations, and  
21 relevance of each study and to integrate evidence as necessary and appropriate based upon strengths,  
22 limitations, and relevance” (Environmental Protection Agency, 2017). This definition is appropriate for  
23 the Clean Air Act as well in addressing causality.

24  
25 The Agency utilizes a weight of evidence framework for causal determination in its Integrated Science  
26 Assessment which includes: a description of the types of scientific evidence used in making  
27 determinations on causality; the key aspects of the evidence evaluation needed to reach causality  
28 conclusions; as well consideration of uncertainty. This approach is not dissimilar to a systematic review,  
29 and most of the principles within the existing framework could be translated to a systematic review  
30 framework. A 2019 publication by Owens et al. also summarizes a framework for assessing causality.  
31 These aspects should be incorporated or referenced by guidance. The criteria for integrating evidence  
32 from epidemiologic, controlled human exposure, and animal toxicological studies (including mode of  
33 action data) should be a key element in the framework. This process should focus on evaluating the  
34 quality of evidence (i.e., human relevancy and adequate exposure characterization to determine effects)  
35 and the consistency in the pattern of effects as well as the strengths, limitations, and uncertainties in the  
36 overall evidence. Currently, the Proposed Rule discussion of concentration-response relationships only  
37 focuses on epidemiology studies and makes no reference to other relevant scientific data that could  
38 inform the determination (e.g., animal studies).

### 39 2.2.3 Evaluating causality

40  
41 There are number of methodologies for evaluating exposure to a chemical and the likelihood of a  
42 particular disease in humans, i.e., what is the evidence that the relationship is causal? In addition, the  
43 available scientific data characterizing aspects of this relationship include epidemiological studies,  
44 whole animal toxicology and biology studies, and in vitro studies utilizing a wide range of sources of  
45 biological materials including tissues, cells, or purified macromolecules. Less frequently, controlled  
46 human studies (e.g., chamber studies with air pollutants) are available. Methods for evaluating causality

1 using specific study types tend to be most strongly developed while characterization across data types is  
2 still ongoing though essential to provide a complete perspective. Board members had a range of  
3 perspectives on methods for evaluating and describing causality that are described here.

#### 4 2.2.4 Evaluation of causality in epidemiology

5  
6 One of the first approaches, presented as a list of postulates, was developed by Sir Bradford Hill in 1965  
7 (Hill, 1965), and was based on the U.S. Surgeon General’s report regarding cigarette smoking and lung  
8 cancer. While the Hill list of postulates relied heavily on findings from epidemiology studies, it also  
9 considered “biological plausibility,” or the need for a mechanistic explanation of findings from  
10 epidemiology studies as part of a causal determination. Since 1965, further approaches to assess  
11 causality (Rhomberg, Bailey, Hamade, & Mayfield, 2011) (Weed, 2005) have been developed. These  
12 analyses provide greater clarity on the need for a reliable mode-of-action (MOA) explanation of findings  
13 from human studies. Sources of MOA understanding typically include findings from animal, in vitro  
14 and in silico studies. In addition to providing insight on causality, MOA also provides insights on the  
15 dose-response relationship, e.g., whether there is a threshold and at what dose such threshold might  
16 exist. In the case of a threshold, causality is not absolute, but is dose-dependent. While a MOA  
17 understanding is a relevant prerequisite for a causality determination, it becomes particularly important  
18 for chemicals with relatively limited epidemiological data sets. As part of a causality determination,  
19 EPA should explicitly present a clearly articulated and comprehensive MOA mode-of-action analysis,  
20 which considers the plausibility of different MOAs, identifies the best-supported MOA, and describes  
21 the potential for dose-dependent causation.  
22

#### 23 2.2.5 Statistical causal analyses

24  
25 Section 83.3(a)(7) calls for selection of endpoints for which there is scientific evidence of a clear causal  
26 (or likely causal) relationship between exposure and effect. While this is reasonable, there is no “one  
27 size fits all” approach to causality; and a variety of approaches may need to be taken.  
28

29 In recent years, there has been an enormous statistical literature on the theme of “causal inference,” see  
30 e.g. the by now classical treatise of Pearl (2009) or the very recent monograph of (Hernan, 2020). Some  
31 serious efforts have been made to apply these methods to determine the impact of NAAQS standards on  
32 health, and the Health Effects Institute (HEI) has sponsored several research programs, often under the  
33 title “Accountability,” in which they have tried to make a direct assessment of the effect of  
34 interventions, sometimes called natural experiments, on air pollution and human health. Reports arising  
35 from HEI studies include (Peters, et al., 2009) (Peel, et al., 2010), (Kelly, et al., 2011a, 2011b) (Noonan,  
36 et al., 2011) (Wong, et al., 2012) (Morgenstern, Harrington, & Shih, 2012) (Zhang, et al., 2013)  
37 (Dockery, et al., 2013) (Zigler, et al., 2016) (Gilliland, et al., 2017) (Russell, et al., 2018). Possibly the  
38 original study of this nature was Pope (1991), who examined the effect on particulate matter (PM10) and  
39 hospital admissions during a several months shutdown of a steel mill in Utah, arguing convincingly that  
40 both PM10 and hospitalizations decreased during this period. However, attempts to reproduce this kind  
41 of result in a variety of alternative contexts have had a mixed record of success.  
42

43 Peel et al. (2010) examined effects in air pollution and emergency department visits of traffic control  
44 measures imposed during the Atlanta Olympic Games in 1996. They noted a reduction in levels of  
45 ozone during the Games, but this was also observed at other locations and may have been due to

1 meteorological changes rather than the traffic control measures. They noted a reduction in emergency  
2 department visits for upper respiratory infections for all age groups and for pediatric ages during the  
3 Olympic Games, but they could not confirm the conclusion of an earlier study that the number of  
4 pediatric emergency care visits for asthma was substantially reduced during the Olympic Games. HEI  
5 noted that the low overall numbers of emergency room admissions and the short duration of the traffic  
6 control measures were limitations to obtaining stronger results in this type of study.

7  
8 Zhang et al. (2013) looked at the effect of control measures that were designed to reduce air pollution  
9 during the 2008 Beijing Olympic Games. They took measurements of a series of air pollutants both  
10 before, during and after the Games, and also measured a series of biomarkers in a group of young and  
11 healthy volunteers. Overall, they found reductions during the Games in several air pollutants, followed  
12 by increases again after the Games had concluded, though ozone did not follow this pattern. They also  
13 showed that these air pollution reductions matched improvements in most biomarkers, though not all.  
14 The HEI Review Committee noted that the study design did not allow the air pollution reductions to be  
15 specifically attributed to the control measures, and also noted the absence of a control sample. A further  
16 comment is that since the effects were measured through biomarkers in health adults, they cannot be  
17 directly related to more serious mortality and morbidity outcomes in susceptible populations.

18  
19 Two studies by Kelly and co-authors (2011a, 2011b) looked at effects of pollution control measures in  
20 London, specifically the Congestion Charging Scheme (CCS) and the Low Emissions Zone (LEZ). The  
21 CCS study (Kelly et al., 2011a) showed potential reductions in air pollution but they were not large  
22 reductions, and difficult to attribute specifically to the CCS. The LEZ study (Kelly et al., 2011b) was a  
23 baseline study carried out in advance of the actual regulation, that examined the potential for detecting  
24 air pollution reductions and also for linking them to medical records. However, again the study had  
25 difficulty demonstrating clear effects and pointed to confidentiality difficulties linking the air pollution  
26 reductions to medical outcomes.

27  
28 Dockery et al. (2013) re-analyzed data from an earlier study on regulatory actions to ban the use of coal  
29 in twelve Irish cities. An earlier study had concluded that these actions led to significant reductions in  
30 total mortality as well as cardiovascular and respiratory mortality. However, when the data were re-  
31 analyzed including comparison cities where the coal bans were not enforced, they concluded that only  
32 for respiratory mortality was there a statistically significant decrease. HEI concluded that “the study  
33 illustrates the considerable challenges faced by this type of analysis in eliminating biases that can lead to  
34 either overestimation or underestimation of the effects of an intervention on public health.”  
35 Among the more convincing recent studies have been the papers of Zigler and co-authors (2012, 2016,  
36 2018) that tried to correlate EPA interventions, i.e., the designation of certain counties or zones as non-  
37 attainment areas under the NAAQS, with improvements in health outcomes in those zones. In particular,  
38 the paper Zigler et al. (2018) won the prestigious 2019 Rothman Epidemiology Prize for its lead author.  
39 However, even that paper stopped short of a clear-cut claim of causality between air pollution control  
40 measures and health benefits:

41  
42 “Results: We found that, on average across all retained study locations, reductions in ambient  
43 PM<sub>2.5</sub> and Medicare health outcomes could not be conclusively attributed to the nonattainment  
44 designations against the backdrop of other regional strategies that impacted the entire Eastern  
45 United States. A more targeted principal stratification analysis indicates substantial health  
46 impacts of the nonattainment designations among the subset of areas where the designations are  
47 estimated to have actually reduced ambient PM<sub>2.5</sub> beyond levels achieved by regional measures,

1 with noteworthy reductions in all-cause mortality, chronic obstructive pulmonary disorder, heart  
2 failure, ischemic heart disease, and respiratory tract infections.”

3  
4 It is established that there are technical difficulties in applying causal inference technology to this kind  
5 of problem. For example, one common assumption made in causal inference is that of no interference  
6 between observational units (also known as the Stable Unit Treatment Value Assumption or SUTVA),  
7 but this is typically not satisfied in the air pollution context, because control measures in one locality  
8 typically affect the air quality in surrounding areas as well (Zigler, Domini, & Wang, 2012).

9  
10 This kind of discussion should not be interpreted as meaning that there is no causal effect, but a formal  
11 proof of causality by statistical methods raises many challenges. In contrast, EPA has for many years  
12 relied on a weight of evidence approach, which is less convincing than formal proof of causality but is  
13 accepted by many epidemiologists.

14  
15 Our recommendation is that EPA should always take causality into account when evaluating  
16 epidemiological evidence, and should especially welcome applications of the statistical field of causal  
17 inference, but should also recognize that there is no “one size fits all” approach to causality, and a  
18 variety of approaches may need to be taken.

19  
20 One SAB member provided a different perspective on causation as follows. For this member, the  
21 relevant type of causation is manipulative (or interventional) causation: Do interventions in fact make  
22 preferred outcomes more probable? This is implied by, but weaker than, mechanistic causation; and it is  
23 stronger than (and does not imply) association-based (Bradford-Hill) causation (Cox, 2018). Relevant  
24 evidence for establishing clear causal or likely to be causal exposure concentration-response (C-R)  
25 relationships includes interventional studies and quasi-experiments with suitable comparison groups.  
26 Manipulative causality cannot be established by associations in observational studies alone (e.g., by  
27 regression models, burden-of-disease models, attributable risk and probability of causation calculations,  
28 relative risks greater than 2, etc.) (Pearl, 2009). The current weight-of-evidence (WoE) framework used  
29 in the National Ambient Air Quality Standards (NAAQS) reviews does not address manipulative  
30 causation. It should be replaced by a framework that does (Cox, 2019). The current WoE framework  
31 attempts to use qualitative criteria to classify evidence of causation. But evidence is continuous, and any  
32 classification system has somewhat arbitrary boundaries (and, in the present system, ambiguous  
33 boundaries). Unambiguous quantitative assessments of evidence for causality should be used instead  
34 (Cox, 2020).

### 35 36 2.2.6 Findings and Recommendations on Estimating Benefits

- 37  
38 • The SAB finds that systematic review principles and approaches provide a transparent and  
39 rigorous approach that should be clearly supported in this rule.
- 40  
41 • The SAB finds that no “one size fits all” approach to causality should be mandated because a  
42 variety of approaches may need to be taken.
- 43  
44 • The SAB recommends that EPA modify the language in Section 82(a)(7) to allow inclusion  
45 in the benefits analyses of effects for which causal or likely causal relationships may be less  
46 certain, but the impact would be substantial.

- The SAB recommends that the Proposed Rule include reference to and support for relevant guidance from current best Agency practices. Relevant guidance includes the systematic review approach developed for the IRIS program and the weight of evidence framework used in the Integrated Science Assessments. Such guidance includes noncancer health effects in the benefits analyses as well as the multiple sources of relevant scientific data (e.g. animal studies, controlled human exposure studies, toxicological studies, including mode of action) in addition to epidemiological data.

### 2.3 **Health Endpoints**

Section 83.3(a)(9) includes proposed requirements pertaining to how the Agency will select concentration-response relationships from the scientific literature for use in quantifying health endpoints in a BCA. In the text below, the SAB offers comments on these requirements and makes recommendations for improvements to the rule regarding how concentration-response functions should be selected for use in a benefit-cost analysis.

The SAB found many of the requirements in this section to be vague and lacking sufficient detail that could impact effective implementation in the BCA. The Proposed Rule also provided limited rationale regarding the scientific basis of including the recommendations. Overall, this section should be revised to provide transparency and clarity regarding: (a) the rationale used to select health endpoints that would be evaluated for a determination of “causal” or “likely” causal; (b) the requirements in section 83.3(a)(9)(ii) through section 83.3(a)(9)(vii) related to suitable study attributes for determining human health impact; (c) how the Agency will ensure consistency with and incorporation of systematic review approaches that have been recommended by the National Academies of Sciences, Engineering and Medicine and the Science Advisory Board; as well as those under development by the EPA in the consolidated Human Health Toxicity Assessment guidelines; and (d) whether any or all of these proposed requirements will be applied across all air pollutants when there are significant regulations. The SAB has provided additional detail related to each of these areas below and recommends that EPA provide more objective and transparent definition associated with the requirements.

#### 2.3.1 **The rationale for health endpoint selection for causality determination**

While the Proposed Rule recommends performing a causality determination and quantifying benefits for those health endpoints with a “causal” or “likely causal” determination it does not provide sufficient detail on the selection of specific health endpoints or the framework for causality determination. The rationale used to select which endpoints are deemed “causal” or “likely causal” is an essential first step in the process for establishing which specific health endpoints will be carried forward for cost benefit analysis. The rule should be revised to provide the specific rationale for endpoint selection. Providing more specific detail will be critical given that some toxicity studies may be considered or evaluated differently with regard to causality determination versus establishing concentration-response functions.

#### 2.3.2 **Clarifying the scientific relevancy and applicability of Section 83.3(a)(9) requirements**

**Science Advisory Board (SAB) Draft Report (09/08/20) – Do Not Cite or Quote.**

**This draft has not been reviewed or approved by the chartered SAB and does not represent EPA policy**

1 Section 83.3(a)(9) of the Proposed Rule provides information on the areas of consideration when the  
2 Agency is selecting and quantifying health endpoints in the BCA. This section should be revised to  
3 provide the rationale for some of the criteria included, the scientific relevancy of the requirements for  
4 informing the regulatory decision, and the applicability of these requirements to the data sets being  
5 evaluated. Recommendations on specific sections are included below:  
6

- 7 • 83.3(a)(9)(ii) – This section focuses on characterizing the sources, extent (range) and  
8 magnitude of uncertainty in quantifying health hazard(s), however this information  
9 appears out of place in this section. The Agency should reorganize and place this  
10 information at the end of this section given its relevancy to section 83.3(a)10 which  
11 focuses on quantitative uncertainty analysis. It also may be useful to highlight in this  
12 section that uncertainties include both the nature of the concentration response functions  
13 as well as assumptions regarding the presence or absence of a concentration-based  
14 threshold above or below which health effects are observed.  
15
- 16 • 83.3(a)(9)(iii)(B) –The Proposed Rule has text which states “...pollutant analyzed in the  
17 study matches the pollutant of interest in the regulation” however it is unclear what  
18 would constitute a “match” (e.g. CAS#, chemical or physical properties). The issue of  
19 determining a “match” relies on scientific judgement that requires more objective and  
20 transparent definition. EPA should provide a clear definition of what would constitute a  
21 match.  
22
- 23 • 83.3(a)(9)(iii)(C) – This section notes that the “Concentration-response functions must be  
24 parameterized from scientifically robust studies.” How is the Agency determining the  
25 robustness of a given study, what criteria are being used and why is “robust” an  
26 appropriate criterion to apply? Instead of including this specific criterion, the Agency  
27 should consider outlining in more general terms the systematic review process informing  
28 the selection and evaluation of the health endpoints. Implementation of criteria and  
29 methods as applied in systematic review processes would provide consistency and  
30 transparency in study selection for the purpose intended.  
31
- 32 • 83.(a)(9)(iii)(D) – The requirements in this section state that a “study location must be  
33 appropriately matched to the analysis” and that “the study population characteristics must  
34 be sufficiently similar to those of the analysis.” While both of these requirements appear  
35 reasonable, there are instances where epidemiological studies from other study locations  
36 (e.g. Canada, Europe) have been deemed relevant for U.S. regulatory decision-making  
37 because of general similarities in demographics and environmental conditions. The  
38 decision regarding whether one study location is “appropriately matched” to another is a  
39 scientific judgment that requires more objective and transparent definition. EPA should  
40 provide a clear definition of what would constitute a study location being appropriately  
41 matched to the analysis.  
42
- 43 • 83.3(a)(9)(iv) – The section should be revised to make clear that the Agency will evaluate  
44 and incorporate the results of positive, negative and null studies into its quantification of  
45 benefits, consistent with the principles of systematic review methods.  
46

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- 83.3(a)(9)(v) – This section should be revised regarding the application and relevance of the technical feasibility criterion. Specifically the Proposed Rule states that “The Agency must base decisions about the choice of the number of alternative concentration-response functions quantified for each endpoint on the extent to which it is technically feasible to quantify alternative concentration-response relationships given the available data and resources.” Technical feasibility is an inadequate criterion and other factors, such as biological plausibility, should also be considered. Notably, Section 83.3(a)(9)(vii)(A) indicates that “plausible alternatives” should be considered, and this suggests that other elements beyond technical feasibility should inform the decision regarding quantification. The Agency’s current efforts to develop Consolidated Human Toxicity Assessment Guidelines may provide a more useful description of elements that can inform decision-making for dose-response analysis.
  - 83.3 (a)(9)(vi) – This section notes that “The Agency must select and clearly identify concentration-response functions with the strongest scientific evidence, as well as evidence necessary to demonstrate the sensitivity of the choice of the concentration-response function on the magnitude and the uncertainty associated with air pollution-attributable effects.” However, since the Agency provides no specific criteria regarding what constitutes the “strongest evidence”; the intent should be clearly defined in the rule and the rule should provide a definition for what is meant by “strongest evidence”.
  - 83.3(a)(9)(vii) – This section provides some specific information regarding what the Agency must characterize (e.g., variability, sensitivities, uncertainties) associated with the concentration-response function. However, there appears to be considerable overlap with other sections of the Proposed Rule that need to be reconciled, revised or eliminated. Some specific comments are included below:
    - The requirement to characterize the variability in the concentration-response functions across studies and models, including plausible alternatives – If different studies of the same phenomenon have used different concentration-response functions, this fact should be noted and some assessment made of how to develop a concentration-response function for the BCA (in other words, EPA should not simply use whichever concentration-response function is most convenient, or what comes closest to some preconceived desirable result). However, it should also be recognized that different studies use different study populations and statistical methods and these do not all have equal weight. Also, even for a single study, some assessment of variability could be made (for example, through standard errors or posterior distributions for the assessed concentration-response function).
    - The requirement to characterize the assumptions, defaults, and uncertainties, their rationale, and their influence on the resulting estimates - It is always appropriate to require that an included study should characterize its assumptions, defaults, uncertainties, and their rationale and influence. This could be viewed as part of the general requirement for transparency in EPA decision making.

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- 1           ○ The requirement to characterize the extent to which scientific literature suggests  
2           that the nature of the effect may vary across demographic or health characteristics  
3           - In cases where scientific literature has considered different demographic or  
4           health characteristics, this fact should be noted and appropriately weighted in the  
5           BCA. However, it should be noted that not all scientific studies include a formal  
6           evaluation of these issues.
- 7
- 8           ○ The requirement to characterize the potential variability of the concentration-  
9           response function over the range in concentrations of interest for the given policy  
10          – it is unclear how this differs from “characterize the variability in the  
11          concentration-response functions” and the Agency should consider combining the  
12          two requirements into one. This requirement may be hinting at issues such as  
13          whether to adopt a linear or non-linear model (for the concentration response  
14          function or some transformation of it, such as a logarithm) and whether to  
15          consider the possible existence of a threshold, but these are issues of scientific  
16          judgment that are difficult to encode in a precise set of rules.
- 17
- 18          ○ The requirement to characterize the influence of potential confounders on the  
19          reported risk coefficient – It is hard to imagine an epidemiological study that does  
20          not consider the effect of potential confounders, but there is ample room for  
21          disagreement over which confounders are appropriate, or how to evaluate an  
22          actual confounding effect (discovery of a confounding effect may raise doubts  
23          about, but need not refute, the claim of a causal effect). The language included in  
24          the propose rule is vague and would be difficult to implement. EPA should  
25          transparently and objectively define how it would characterize the influence of  
26          potential confounders.
- 27
- 28          ○ The requirement to characterize the likelihood that the parameters of the  
29          concentration-response differ based on geographic location – This is a good idea  
30          in principle but many epidemiological studies do not explicitly provide  
31          information that would inform this requirement and as such may result in the  
32          exclusion of well conducted and relevant studies.
- 33
- 34          ○ The requirement to characterize the attributes that affect the suitability of the  
35          study or model for informing a risk assessment, including the age of the air  
36          quality data, and the generalizability of the study population – This section and  
37          section 83.3(a)(9)(iii) both discuss some study attributes that need to be  
38          considered. In those instances, the rule would benefit if the Agency clearly  
39          characterized the attributes that affect the suitability of the study or model for  
40          informing a hazard assessment and the quantification of benefits. Notably, in this  
41          section it is unclear what the Agency means by “age of the air quality data” or  
42          what criteria would be used to determine the relevance of a study for decision-  
43          making.
- 44

45          While the SAB has offered specific recommendations on the sections noted above, the Agency  
46          should consider replacing all the specific criteria in sections 83.3(a)(9)(ii) and 83.3(a)(9)(vii)  
47          with an overall framework outline of the systematic review principles it would follow for the

1 evaluation of human health hazard data for the purposes of concentration-response selection and  
2 quantification of benefits. This overall discussion of systematic review approaches could for  
3 example include requirements that studies used be subject to external peer review, including a  
4 critical review of the reliability of both hazard endpoints and exposure metrics reported, account  
5 for potential confounders/co-exposures on study findings, and ensure the relevance of study  
6 attributes in supporting subsequent benefit cost analysis calculations (e.g. representative location  
7 and population characteristics in epidemiology studies).  
8

### 9 2.3.3 Consistency and incorporation of best available and relevant systematic review 10 approaches

11  
12 As the Agency is considering best practices and approaches for the selection and evaluation of health  
13 endpoints for use in the benefit cost analysis, it must ensure consistency with current EPA approaches  
14 and recommendations of the scientific community. Section (a)(9) provides no information regarding  
15 how current Agency practices and advice it has received from scientific review boards on data  
16 identification, evaluation and integration are being applied to the BCA. For example, the Proposed Rule  
17 provides no discussion of ongoing EPA efforts that have been supported by the Science Advisory Board,  
18 or the National Academy of Sciences, Engineering and Medicine (NASEM) related to the use of  
19 systematic review. The Proposed Rule also does not appear to align with the Agency’s plans to develop  
20 Consolidated Human Toxicity Assessment Guidelines. The rule should be revised to include a  
21 discussion regarding how the Agency will ensure that relevant NASEM and SAB advice on systematic  
22 review as well as EPA’s Consolidated Human Toxicity Assessment Guidelines will be evaluated and  
23 incorporated. Additionally, the Proposed Rule provides no discussion regarding whether relevant peer  
24 reviewed publications that provide suggested systematic review approaches (Simon, Zhu, & Dourson,  
25 2016) (Suter, Cormier, & and Barron, 2017) (Wikoff, Urban, & Harvey, 2018) (Wikoff, Rager,  
26 Chappell, Fitch, & Haws, 2019) which describe how to assess uncertainty, variability and data quality  
27 evaluation in systematic review for the derivation of toxicity values were evaluated to inform the  
28 Proposed Rule. The Agency is encouraged to review and incorporate by reference or specific language  
29 relevant best practices.  
30

### 31 2.3.4 Applicability of proposed requirements for various air pollutants

32  
33 As currently written, section (a)(9) does not provide sufficient clarity regarding what types of air  
34 pollutant regulation these rule requirements would apply. Specifically, the SAB recommends that this  
35 section be revised to provide clear direction regarding whether it is the Agency’s intent that these  
36 scientific requirements broadly apply across all air pollutants for which EPA may develop significant  
37 regulation. The Agency should also consider providing the specific sections of the Clean Air Act to  
38 which these proposed requirements for quantifying health endpoints would apply (e.g., criteria  
39 pollutants regulated with National Ambient Air Quality Standards, hazardous air pollutants).  
40  
41  
42  
43

1       2.3.5   **Findings and Recommendations on the Selection of Health Endpoints**

- 2
- 3       • The SAB finds many of the requirements associated with the selection of health endpoints in
- 4       the Proposed Rule to be vague and lacking sufficient detail that could impact effective
- 5       implementation in the BCA.
- 6
- 7       • The SAB recommends the Proposed Rule be revised to clearly include what types of air
- 8       pollutant regulations are covered under the rule.
- 9
- 10      • The Proposed Rule should be revised to clearly provide the specific scientific rationale for
- 11      endpoint selection, and transparently define specific terms used in the requirements, or the
- 12      Agency should replace all of the specific criteria on the selection of health endpoints with an
- 13      overall framework outline of the systematic review principles it would follow for the
- 14      evaluation of human health hazard data for the purposes of concentration-response selection
- 15      and quantification of benefits.
- 16
- 17      • The Proposed Rule should be revised to include a discussion of how the Agency will ensure
- 18      that relevant advice from NASEM and the SAB on systematic review as well as EPA’s
- 19      Consolidated Human Toxicity Assessment Guidelines will be evaluated and incorporated.
- 20

21

22   2.4   **Characterizing Uncertainty**

23

24   Section 83.3(a)(10) of the Proposed Rule establishes requirements for characterizing uncertainties

25   underlying the estimation of both benefits and costs. In this section we discuss several places where the

26   Proposed Rule or its preamble depart from best practices and provide recommendations for

27   improvement.

28

29       2.4.1   **The Purposes of Uncertainty Analysis**

30

31   Uncertainty analysis is a critical and long-standing part of benefit-cost analysis (BCA). Best practices

32   for carrying it out are discussed in detail in both EPA’s *Guidelines for Preparing Economic Analyses*

33   and in OMB’s Circular A-4.

34

35   Uncertainty analysis serves several important purposes when applied in the evaluation of proposed air

36   rules. First, it allows analysts to determine the robustness of a BCA’s results by systematically

37   evaluating the range of possible outcomes and their likelihoods. A careful uncertainty analysis will

38   indicate whether the BCA is relatively precise, with a narrow range of possible outcomes, or less

39   precise, with a broad range of outcomes and potentially much larger or smaller net benefits than

40   expected. The range of outcomes, in turn, will indicate whether the overall finding of the BCA—that is,

41   whether the rule produces positive or negative net benefits—is robust to plausible variations in the

42   BCA’s assumptions. Providing this information to policy makers and the public is an important part of

43   transparency in rule-making. The preamble to the Proposed Rule focuses on this aspect of uncertainty

44   analysis.

45

1 However, a second purpose of uncertainty analysis, which is not discussed in the rule’s preamble, is to  
2 guide future scientific research beyond the immediate analysis of the rule. Specifically, the analysis will  
3 indicate which underlying uncertainties contribute most to the uncertainty in overall net benefits. As  
4 discussed in both Circular A-4 and EPA’s *Guidelines*, when the level of uncertainty is large, a formal  
5 value of information analysis could be applied to determine where additional scientific research would  
6 be most valuable. It could even be used to determine whether a decision should be deferred until better  
7 information can be obtained. In some cases, the additional research will take the form of new studies and  
8 data collection; in other cases, it may involve refining the existing analysis by eliminating poor studies  
9 that are biased, are missing confounders, use poor statistical analysis, or have overstated results, and  
10 then finding improved ways to combine what is left.

11  
12 A third purpose of the analysis, which is only tangentially discussed in the rule and its preamble, is to  
13 help policy makers and the public understand possible outcomes that may be far from the expected value  
14 of the rule. In particular, in contexts involving low-probability risks of catastrophic losses, policy  
15 makers and members of the public may wish to consider policies that reduce the likelihood of severe  
16 losses even though doing so may mean accepting a lower expected payoff. Moreover, understanding the  
17 range of possible outcomes can provide useful information even in the absence of catastrophic losses if  
18 the distribution of benefits is skewed. For example, the analysis could indicate that a rule has relatively  
19 little downside risk (a relatively narrow range of outcomes worse than its expected value) and relatively  
20 large upside risk (a relatively large range of potentially better outcomes), or vice versa. Characterizing  
21 the range of outcomes is critical: BCA is a tool to help policy makers and the public understand the  
22 possible consequences of policies, not a decision rule dictating that policy choices should be made solely  
23 on the basis of expected value.

#### 24 25 2.4.2 Alignment of the Proposed Rule with Best Practices

26  
27 Although uncertainty analysis is a key part of a BCA, the Proposed Rule departs from best practices in  
28 two respects.

29  
30 First, both Circular A-4 and EPA’s *Guidelines* recommend that the scope and extent of an uncertainty  
31 analysis be appropriate for the policy context. The Proposed Rule is insufficiently clear on this point. As  
32 written, it seems to suggest that EPA rigidly follow a prescribed set of steps that could be overly onerous  
33 or have little value for some rules.

34  
35 In some cases, the rule could lead to EPA devoting resources to the uncertainty analysis that would be  
36 better spent on refining the underlying science. Even the most rigorous uncertainty analysis will be  
37 unable to correct errors resulting from the inclusion of poor science in a BCA. Identifying and removing  
38 such studies is likely to have a greater impact on the quality of a BCA than uncertainty analysis.  
39 EPA should address this issue by revising the rule to indicate explicitly that analysts have some  
40 discretion in designing and carrying out the analysis. In particular, the Proposed Rule explicitly expands  
41 the domain of policies subject to BCA beyond those previously considered “significant” under Section  
42 3(f) of Executive Order (EO) 12866 (Clinton, 1993). The existing class of significant rules already  
43 varies enormously in importance to the environment, the economy, and overall public wellbeing.  
44 Sometimes under EO 12866 a rule is declared significant simply because it includes a novel legal  
45 interpretation rather than important environmental or economic impacts. Under the new interpretation,  
46 the range of policies to be evaluated will be even broader. As a result, the agency should reconsider

1 whether requiring the same degree of complexity in the uncertainty analysis of every policy is  
2 appropriate.

3  
4 Moreover, as written the Proposed Rule recommends formal probabilistic uncertainty analysis for all  
5 policies deemed significant under the rule’s expanded definition of the term. However, both Circular A-  
6 4 and EPA’s *Guidelines* only recommend probabilistic analysis for economically significant rules with  
7 impacts larger than \$1 billion per year: both agencies regard a deterministic sensitivity analysis to be  
8 adequate for rules with lower impacts. The Agency should explain why the broader application of  
9 probabilistic analysis has been judged appropriate or, alternatively, it should consider using the \$1  
10 billion threshold to determine when some of the more intensive methods of uncertainty analysis, such as  
11 probabilistic analysis, are required.

12  
13 The rule’s second departure from best practices is that it may lead analysts to focus too heavily on the  
14 expected value of a policy and not give adequate attention to other values in the range of likely  
15 outcomes. As noted above, a BCA should provide policy makers and the public with broader  
16 information: the expected value of a policy is rarely the only criterion for a decision. In fact, BCA is  
17 often most valuable when uncovering marginal impacts of policy options such as inclusion of a  
18 subsector of industry or adjustments in the policy’s timing. Moreover, focusing heavily on expected  
19 value will be particularly inappropriate when there are thought to be significant unquantified benefits or  
20 costs. This could be addressed by revising subsection (vi) to increase its emphasis on outcomes beyond  
21 the expected value, and to note the need for acknowledging unquantified benefits or costs, where  
22 appropriate.

### 23 24 2.4.3 Recommendations on Uncertainty Analysis

- 25  
26 • The preamble should be revised to discuss the broader purposes of uncertainty analysis beyond  
27 simple transparency.
- 28  
29 • In several places the Proposed Rule should be revised to align it with best practices, which  
30 require that the analysis be appropriate for the policy context. This can largely be done by  
31 replacing the words “to the extent feasible” with “to the extent feasible and appropriate”.
- 32  
33 • The discussion in section (vi) should be broadened to reflect the fact that outcomes other than the  
34 expected value may be very important for policies involving low-probability, high-consequence  
35 hazards. Also, when presenting quantitative results EPA should also clearly note when there are  
36 unquantified benefits or costs that could be significant.
- 37  
38 • The discussion should note that uncertainty analysis will not correct errors resulting from the  
39 inclusion of poor science, which arguably has a greater impact on policy choices.

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## REFERENCES

- Clewell, HJ and Crump, KS. (2005, April). Quantitative estimates of risk for noncancer endpoints. *Risk Analysis*, 285-289. doi:10.1111/j.1539-6924.2005.00589.x
- Clinton, W. J. (1993, September 30). *Executive Order 12866 of September 30, 1993: Regulatory Planning and Review*. Retrieved from Federal Register Archives: <https://www.archives.gov/files/federal-register/executive-orders/pdf/12866.pdf>
- Cox, L. (1984, September). Probability of Causation and the Attributable Proportion Risk. *Risk Analysis*, 4(3). Retrieved from <https://doi.org/10.1111/j.1539-6924.1984.tb00142.x>
- Cox, L. (2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. *Critical Review of Toxicology*, 48(8), 682-712. doi:10.1080/10408444.2018.1518404
- Cox, L. (2019, November). Improving Causal Determination. *Global Epidemiology*, 1-7. Retrieved from <https://doi.org/10.1016/j.gloepi.2019.100004>
- Cox, L. (2020, August). Implications of nonlinearity, confounding, and interactions for estimating exposure concentration-response functions in quantitative risk analysis. *Environmental Research*, 187. doi:10.1016/j.envres.2020.109638
- Dockery, D., Rich, D., Goodman, P., Clancy, L., Ohman-Strickland, P., George, P., & and Kotlov, T. (2013). *Effect of Air Pollution Control on Mortality and Hospital Admissions in Ireland*. Research Report 176, Boston, MA. Retrieved from <https://www.healtheffects.org/publication/effect-air-pollution-control-mortality-and-hospital-admissions-ireland>
- Environmental Protection Agency. (2010, Updated 2014). *Guidelines for Preparing Economic Analyses*. National Center for Environmental Economics. Retrieved from <https://www.epa.gov/sites/production/files/2017-08/documents/ee-0568-50.pdf>
- Environmental Protection Agency. (2015). Preamble to the Integrated Science Assessments (ISA). Washington DC: EPA/600/r-15/067. Retrieved from [cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244](https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244)
- Environmental Protection Agency. (2017, July 20). Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act. 82(138), 33726. Federal Register. Retrieved from <https://www.govinfo.gov/content/pkg/FR-2017-07-20/pdf/2017-14337.pdf>
- Environmental Protection Agency. (2017, July 20). Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act. *Federal Register*, 82(138), 33733.
- Environmental Protection Agency. (2020, June 11). Increasing Consistency and Transparency in Considering Benefits and Costs in the Clean Air Act Rulemaking Process. *Federal Register*, 85(113), 35612-35627.
- Gilliland, F., Avol, E., McConnell, R., Berhane, K., Gauderman, W., Lurmann, F., . . . Rappaport, E. a. (2017). *The Effects of Policy-Driven Air Quality Improvements on Children's Respiratory Health*. Boston, MA: Health Effects Institute. Retrieved from <https://www.healtheffects.org/publication/effects-policy-driven-air-quality-improvements-childrens-respiratory-health>
- Hernan, M. a. (2020). *Causal Inference: What If*. Boca Raton, FL: Chapman & Hall/CRC.
- Hill, A. (1965). The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*, 58(5), 295-300.

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- 1 Kelly, F., Anderson, H., Armstrong, B., Atkinson, R., Barratt, B., Beevers, S., . . . Green, D. (2011). *The*  
2 *Impact of the Congestion Charging Scheme on Air Quality in London*. Research Report 155,  
3 Boston, MA. Retrieved from [https://www.healtheffects.org/publication/impact-congestion-](https://www.healtheffects.org/publication/impact-congestion-charging-scheme-air-quality-london)  
4 [charging-scheme-air-quality-london](https://www.healtheffects.org/publication/impact-congestion-charging-scheme-air-quality-london)
- 5 Kelly, F., Armstrong, B., Atkinson, R., Anderson, H., Barratt, B., Beevers, S., . . . Wilkinson, P. (2011).  
6 *The London Low Emissions Zone Baseline Study*. Health Effects Institute. Retrieved from  
7 <https://www.healtheffects.org/search/site/research%20report%20148>
- 8 McGartland, A., Revesz, R., Axelrad, D., Dockins, C., Sutton, P., & Woodruff, T. (2017).  
9 Estimating the health benefits of environmental regulations. *Science*, 357, 457-458.  
10 doi:10.1126/science.aam8204
- 11 Morgenstern, R., Harrington, W., & Shih, J.-S. a. (2012). *Accountability Analysis of Title IV Phase 2 of*  
12 *the 1990 Clean Air Act Amendments*. Boston, MA: Health Effects Institute. Retrieved from  
13 [https://www.healtheffects.org/publication/accountability-analysis-title-iv-phase-2-1990-clean-](https://www.healtheffects.org/publication/accountability-analysis-title-iv-phase-2-1990-clean-air-act-amendments)  
14 [air-act-amendments](https://www.healtheffects.org/publication/accountability-analysis-title-iv-phase-2-1990-clean-air-act-amendments)
- 15 National Academies of Sciences, Engineering and Medicine. (2019). *Evaluation of the Protocol for the*  
16 *IRIS Toxicological Review of Inorganic Arsenic*. Washington DC: The National Academies  
17 Press. doi:<https://doi.org/10.17226/25558>
- 18 National Academy of Sciences, Engineering and Medicine. (2018). *Progress Toward Transforming the*  
19 *Integrated Risk Information (IRIS) Program: A 2018 Evaluation*. Washington, DC: The National  
20 Academies Press. doi:<https://doi.org/10.17226/25086>
- 21 Noonan, C., Ward, T., Navidi, W., Sheppard, L., Bergauff, M., & Palmer, C. (2011). *Assessing the*  
22 *Impact of a Wood Stove Replacement Program on Air Quality and Children's Health*. Research  
23 Report 162, Boston, MA. Retrieved from  
24 <https://www.healtheffects.org/search/site/research%20report%20162>
- 25 Office of Management and Budget. (2003). Regulatory Analysis. Retrieved from  
26 [https://obamawhitehouse.archives.gov/omb/circulars\\_a004\\_a-4/](https://obamawhitehouse.archives.gov/omb/circulars_a004_a-4/)
- 27 Owens, E., Patel, M., Kirrane, E., Long, T., Brown, J., Cote, I., . . . and Dutton, S. (2017). Framework  
28 for assessing causality of air pollution-related health effects for review of the National Ambient  
29 Air Quality Standards. *Regulatory Toxicology and Pharmacology*, 88, 332-337.
- 30 Pearl, J. (2009). Causal inference in statistics: An Overview. *Statistics Surveys*, 3, 96-146. Retrieved  
31 from [projecteuclid.org/euclid.ssu/1255440554](http://projecteuclid.org/euclid.ssu/1255440554)
- 32 Peel, J., Flanders, W., Mulholland, J. T., & Klein, M. (2010). *Impact of Improved Air Quality During the*  
33 *1996 Summer Olympic Games in Atlanta on Multiple Cardiovascular and Respiratory*  
34 *Outcomes*. Boston, MA: Health Effects Institute. Retrieved from  
35 <https://www.healtheffects.org/search/site/research%20report%20148>
- 36 Peters, A., Brietner, S., Cyrus, J., Stolzel, M., Pitz, M., Wolke, G., . . . and Wichmann, H. (2009). *The*  
37 *Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany*. Boston, MA: Health  
38 Effects Institute. Retrieved from [https://www.healtheffects.org/publication/influence-improved-](https://www.healtheffects.org/publication/influence-improved-air-quality-mortality-risks-erfurt-germany)  
39 [air-quality-mortality-risks-erfurt-germany](https://www.healtheffects.org/publication/influence-improved-air-quality-mortality-risks-erfurt-germany)
- 40 Pope, C. (1991). Respiratory hospital admissions associated with PM10 pollution in Utah, Salt Lake and  
41 Cache Valleys. *Archives of Environmental Health*, 46(2), 90-97. Retrieved from  
42 <https://www.tandfonline.com/doi/abs/10.1080/00039896.1991.9937434>
- 43 Rhomberg, L., Bailey, L. G., Hamade, A., & Mayfield, D. (2011). Is exposure to formaldehyde in air  
44 causally associated with leukemia? - A hypothesis-based weight-of-evidence analysis. *Critical*  
45 *Review of Toxicology*, 41(7), 555-621.  
46

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- 1 Russell, A., Tolbert, P., Henneman, L., Abrams, J., Liu, C., Klein, M., . . . Shen, H. a. (2018). *Impacts of*  
2 *Regulations on Air Quality and Emergency Department Visits in the Atlanta Metropolitan Area,*  
3 *1999-2013.* Boston, MA: Health Effects Institute. Retrieved from  
4 [https://www.healtheffects.org/publication/impacts-regulations-air-quality-and-emergency-](https://www.healtheffects.org/publication/impacts-regulations-air-quality-and-emergency-department-visits-atlanta-metropolitan)  
5 [department-visits-atlanta-metropolitan](https://www.healtheffects.org/publication/impacts-regulations-air-quality-and-emergency-department-visits-atlanta-metropolitan)
- 6 Simon, T., Zhu, Y., & Dourson, M. a. (2016). Bayesian methods for uncertainty factor application for  
7 derivation of reference values. *Regulatory Toxicology and Pharmacology*, *13*(6), 9-24.
- 8 Suter, G., Cormier, S., & and Barron, M. (2017). A weight of evidence framework for environmental  
9 assessments: inferring qualities. *Integrated Environmental Assessment and Management*, *13*(6),  
10 1038-1044.
- 11 Weed, D. (2005). Weight of evidence: A review of concepts and methods. *Risk Analysis*, *26*(6), 1545-  
12 1557.
- 13 Wheeler, A. R. (2020, February 20). *Memorandum on Science Advisory Board Engagement Process for*  
14 *Review of Regulatory Actions.* Retrieved from  
15 [https://yosemite.epa.gov/sab/sabproduct.nsf/WebBOARD/RegReviewProcess/\\$File/SAB%20En](https://yosemite.epa.gov/sab/sabproduct.nsf/WebBOARD/RegReviewProcess/$File/SAB%20Engagement%20Process%20re%20Regulatory%20Actions.pdf)  
16 [gagement%20Process%20re%20Regulatory%20Actions.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/WebBOARD/RegReviewProcess/$File/SAB%20Engagement%20Process%20re%20Regulatory%20Actions.pdf)
- 17 Wikoff, D., Rager, J., Chappell, G., Fitch, S., & Haws, L. a. (2019). A framework for systematic  
18 evaluation and quantitative integration of mechanistic data in assessments of potential human  
19 carcinogens. *Toxicological Sciences*, *167*(2), 322-335.
- 20 Wikoff, D., Urban, J., & Harvey, S. a. (2018). Role of risk bias in systematic review for chemical risk  
21 assessment: a case study in understanding the relationship between congenital heart defects and  
22 exposures to trichloroethylene. *International Journal of Toxicology*, *37*(2), 125-143.
- 23 Wong, C., Rabl, A., Thach, T., Chau, Y., Chan, K., Cowling, B., . . . Anderson, H. a. (2012). *Impact of*  
24 *the 1990 Hong Kong Legislation for Restriction on Sulfur Content in Fuel.* Health Effects  
25 Institute. Retrieved from [https://www.healtheffects.org/publication/impact-1990-hong-kong-](https://www.healtheffects.org/publication/impact-1990-hong-kong-legislation-restriction-sulfur-content-fuel)  
26 [legislation-restriction-sulfur-content-fuel](https://www.healtheffects.org/publication/impact-1990-hong-kong-legislation-restriction-sulfur-content-fuel)
- 27 Zhang, J., Zhu, T., Kipen, H., Wang, G., Huang, W., Rich, D., . . . and Thomas, D. (2013).  
28 *Cardiorespiratory Biomarker Responses in Healthy Young Adults to Drastic Air Quality*  
29 *Changes Surrounding the 20087 Beijing Olympics.* Boston, MA: Health Effects Institute.  
30 Retrieved from [https://www.healtheffects.org/publication/cardiorespiratory-biomarker-](https://www.healtheffects.org/publication/cardiorespiratory-biomarker-responses-healthy-young-adults-drastic-air-quality-changes)  
31 [responses-healthy-young-adults-drastic-air-quality-changes](https://www.healtheffects.org/publication/cardiorespiratory-biomarker-responses-healthy-young-adults-drastic-air-quality-changes)
- 32 Zigler, C., Choirat, C., & Domini, F. (2018). Impact of National Ambient Air Quality Standards  
33 Nonattainment Designations on Particulate Pollution and Health Pollution and Health.  
34 *Epidemiology*, 165-174. Retrieved from  
35 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5792368/>
- 36 Zigler, C., Domini, F., & and Wang, Y. (2012). Estimating causal effects of air quality regulations using  
37 principal stratification for spatially correlated multivariate intermediate outcomes. *Biostatistics*,  
38 289-302. doi:10.1093.biostatistics/kxr052
- 39 Zigler, C., Kim, C., Choirat, C., Hansen, J., Wang, W., Hund, L., . . . King, G. a. (2016). *Causal*  
40 *Inference Methods for Estimating Long-Term Health Effects of Air Quality Regulations.* Boston,  
41 MA: Health Effects Institute. Retrieved from [https://www.healtheffects.org/publication/causal-](https://www.healtheffects.org/publication/causal-inference-methods-estimating-long-term-health-effects-air-quality-regulations)  
42 [inference-methods-estimating-long-term-health-effects-air-quality-regulations](https://www.healtheffects.org/publication/causal-inference-methods-estimating-long-term-health-effects-air-quality-regulations)

43