ORAL ARGUMENT NOT YET SCHEDULED

No. 23-1045 (consolidated with Nos. 23-1085 and 23-1047)

IN THE UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF COLUMBIA CIRCUIT

HUNTSMAN PETROCHEMICAL L.L.C., ET AL.,
Petitioners,

v.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,
Respondent.

On Petitions for Review of Final Actions
of the United States Environmental Protection Agency

FINAL BRIEF OF AMICUS CURIAE TEXAS COMMISSION ON ENVIRONMENTAL QUALITY IN SUPPORT OF PETITIONERS

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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES*

The following information is provided pursuant to D.C. Circuit Rule 28(a)(1):

(A) Parties and Amici

All parties, intervenors, and amici appearing in this Court are identified in the petitioners' opening brief.

(B) Rulings Under Review

References to the rulings at issue appear in the petitioners' opening brief.

(C) Related Cases

References to related cases appear in the petitioners' opening brief.

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* As a governmental entity, the Commission is not subject to the disclosure requirements of Federal Rule of Appellate Procedure 26.1.

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2016 IRIS	EPA's Integrated Risk Information System program (2016)
Rule	National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review, 85 Fed. Reg. 49,084 (Aug. 12, 2020)
Proposed Reconsideration	Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants, 87 Fed. Reg. 6,466 (Feb. 4, 2022) (proposed rule)
Reconsideration Decision	Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants, 87 Fed. Reg. 77,985 (Dec. 21, 2022) (final rule)
Akaike value	Akaike information criterion value
APA	Administrative Procedure Act
AR	Administrative record (The "AR" documents cited in this brief are from EPA docket number EPA-HQ-OAR-2018-0746. They are identified by their final four digits on EPA's docket.)
Board	EPA's Science Advisory Board
Commission	Texas Commission on Environmental Quality
EPA	United States Environmental Protection Agency
Institute	National Institute for Occupational Safety and Health
P-value	Probability value

STATUTES AND REGULATIONS

The relevant statutes and regulations appear in the petitioners' addendum.

Statement of Identity of Amicus, Interest in Case, and Source of Authority to File

The Commission, which implements the federal Clean Air Act and its Texas counterpart, submits this amicus brief in accordance with D.C. Circuit Rule 29(a)(2). The challenged EPA actions directly affect the Commission's regulation of air quality, and the Commission has special expertise with respect to the issues presented. All parties have consented to the filing of this brief. *See* Doc. 2005376 at 1.

Statement of Authorship and Financial Contribution

In accordance with D.C. Circuit Rule 29(a)(4)(E), the Commission states that it is the sole author of and contributor to this brief. No counsel for any party authored this brief, in whole or in part. No person or entity other than the Commission contributed monetarily to its preparation or submission.

Introduction

The Clean Air Act requires EPA to set emissions standards for hazardous air pollutants. The standards strike a balance between protecting public health and burdening essential industry.

Here, EPA overestimated the health risks associated with ethylene oxide, a compound used to sterilize medical equipment. It did so notwithstanding the Commission's recent, accurate, and peer-reviewed risk assessment.

EPA erred in several ways, two of which are independently dispositive. *First*, EPA ignored evidence that its risk-assessment model was less accurate than the Commission's. And instead of addressing the Commission's concerns, EPA doubled down on points the Commission had already refuted. *Second*, EPA assessed whether ethylene oxide causes breast cancer based on a pair of studies that failed to account for an important aspect of the problem—namely, whether the women in the studies were more likely to develop breast cancer in the first place based on how many children they had. For those reasons, the Rule and the Reconsideration Decision should be set aside or reversed as arbitrary and capricious.

Supplemental Statement of the Case

I. Overview

The Clean Air Act requires EPA to regulate emissions of hazardous air pollutants and adopt emission standards to minimize the health risks they pose. 42 U.S.C. § 7412(d), (f). The standards balance the need to mitigate risk with the costs of

compliance. *See* National Emission Standards for Hazardous Air Pollutants, 68 Fed. Reg. 63,852, 63,852 (Nov. 10, 2003).

The standards that target miscellaneous organic chemical manufacturing facilities are called "MON rule[s]" for short. *See, e.g.*, Rule, 85 Fed. Reg. at 49,111 (JA 1408). Among other things, MON rules establish design specifications for storage tanks and equipment-leak cleanup requirements, and they also limit overall emissions of hazardous air pollutants. *See* 68 Fed. Reg. at 63,854.

In the Rule, EPA determined the health risks associated with ethylene oxide and altered requirements for storage tanks and other equipment used to handle it. *See* 85 Fed. Reg. at 49,088-89 (JA 1385-86). Ethylene oxide is an organic compound used to manufacture antifreeze, plastics, adhesives, and other common products. *See* AR-0303, Attachment A at 10 (JA 3660). It is also used to sterilize medical equipment. *Id.*

As with many things, though, there is a tradeoff. A gas at room temperature, ethylene oxide may be inhaled by the people who work around it, increasing their risk of developing cancer. AR-0303, Attachment A at 6, 10 (JA 3656, 3660). A significant percentage of commercial ethylene oxide is produced at fifteen facilities, most of them in Texas and Louisiana. *Id.* at 10 (JA 3660). This case concerns EPA's determination of the risk level posed by ethylene-oxide exposure at those and other facilities.

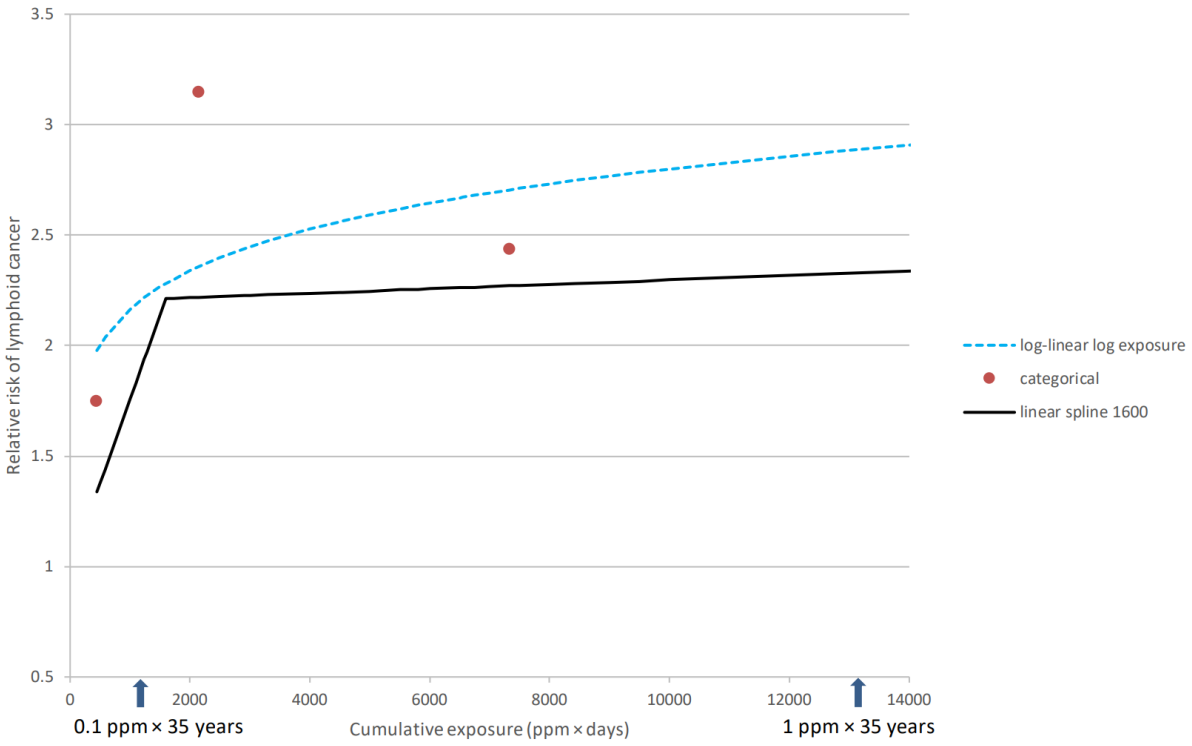
II. Factual and Procedural Background

A. EPA's determination of the health risks posed by ethylene oxide

In assessing ethylene-oxide risk, EPA relied on a 2016 model produced by the agency's Integrated Risk Information System ("2016 IRIS"). *See* Rule, 85 Fed. Reg. at 49,102 (JA 1399). The 2016 IRIS estimated the cancer risk posed by inhalation of the compound, *see id.* at 49,097-98 & n.10, 49,128 n.7 (JA 1394-95, 1425), and indicated that ethylene-oxide exposure increases the risk of developing both lymphohematopoietic cancer (which is also called lymphoid cancer) and breast cancer, AR-0202 at 1-1 (JA 2299). Two key numbers in the study were the amount of ethylene oxide that people were exposed to over time and the number of people who died of cancer. *See id.* at 4-99 to 4-101 (JA 2480-82).

The 2016 IRIS's risk estimate was based on a mathematical formula called a two-piece linear spline model. *Id.* at 1-2 (JA 2300). In a linear model, the relationship between or among data is reflected in a single line. *See, e.g.*, Nicholas P. Jewell, Statistics for Epidemiology 190-94 (2004) (ebook). In a two-piece linear spline, the line is broken into two segments; the point at which the segments meet is called a knot. Miquel Porta, Spline Models, A Dictionary of Epidemiology 267 (6th ed. 2016). A knot's location may be either "fix[ed]"—that is, based on expert judgment, rather than statistical data analysis—or mathematically "estimat[ed] . . . from the data." AR-0258 at 12 (JA 3324).

The two-piece linear spline that EPA relied on here is represented by the solid line on this graph:



AR-0202 at 4-103 (JA 2484). The knot is the point at which that line changes direction.

The underlying data for the 2016 IRIS risk value came from records compiled by the National Institute for Occupational Safety and Health, which studied workers who used ethylene oxide to sterilize medical equipment. AR-0202 at 4-3 (JA 2384). The study was large. It encompassed approximately 17,500 people, more than half of them women, who worked at thirteen sterilizing facilities. *Id.*

B. The Commission's risk assessment

The Commission prepared its own ethylene-oxide risk assessment. *See* Rule, 85 Fed. Reg. at 49,097 (JA 1394). It agreed with EPA that ethylene-oxide inhalation increases the risk of lymphoid cancer, but it disagreed as to the degree of that risk.

See AR-0303, Attachment A at 1 (JA 3651). And it found the data insufficient to support a link between ethylene-oxide exposure and breast cancer. *Id.*

The Commission also concluded that the 2016 IRIS overestimated the overall cancer risk. *See* Proposed Reconsideration, 87 Fed. Reg. at 6,469-70 (JA 3135-36). To reach that conclusion, the Commission analyzed the same Institute data, but it also ran those data through a different mathematical formula called a "Cox regression" model. AR-0303, Attachment A at 1-2 (JA 3651-52). The Commission's Cox regression model charted the relationship between exposure to different amounts of ethylene oxide over time and the number of fatalities resulting from lymphoid cancer in the Institute's data set. *See* AR-0303, Attachment A at 51-52 (JA 3701-02).

C. The challenged Rule and Reconsideration Decision

EPA based the Rule on the 2016 IRIS risk level. *See* Proposed Reconsideration, 87 Fed. Reg. at 6,469 (JA 3135); Rule, 85 Fed. Reg. at 49,097 (JA 1394). In finalizing the Rule, EPA rejected comments asserting that the Commission's risk assessment was more accurate. *See* Rule, 85 Fed. Reg. at 49,097-98 (JA 1394-95). Indeed, EPA refused to consider the Commission's assessment because it was still in the draft phase at the close of the Rule's comment period. *Id.* at 49,098 (JA 1395).

By the time the Rule was published, though, the Commission had finalized its risk assessment. *Id.* at 49,098 n.12 (JA 1395). Several interested parties filed reconsideration petitions asking EPA to take that assessment into account. Proposed Reconsideration, 87 Fed. Reg. at 6,469-70 (JA 3135-36). EPA agreed to do so, calling for comments on whether it should continue using the 2016 IRIS value or instead use the Commission's alternative risk assessment. *Id.* at 6,470 (JA 3136). In the

Reconsideration Decision, EPA opted to stick with the 2016 IRIS value. 87 Fed. Reg. at 77,989, 77,991 (JA 4102, 4104). Several petitioners timely sought this Court's review of the Rule and the Reconsideration Decision. *See* Petitioners' Opening Br. 1. The Commission files this amicus brief supporting the challenges to those actions.

Summary of the Argument

I. At best, EPA's decision to prefer the 2016 IRIS value over the Commission's risk assessment is insufficiently supported by the record. At worst, it is contrary to the evidence before the agency. Either of those conclusions would support a judgment setting aside or reversing the Rule and the Reconsideration Decision.

The Commission commented on two basic indicators of model accuracy. The first is whether a model can predict the number of cancer deaths recorded in the underlying data. The second is whether essential calculations are supported by other calculations that mathematicians use to check their work. On the first point, the Commission evaluated both its own risk assessment and the 2016 IRIS and found its risk assessment to be far more accurate. On the second, the Commission identified a calculation error that skewed the results that EPA relied on.

EPA did not adequately account for either of those important aspects of the problem. It instead offered explanations that were unsupported by the administrative record. It argued, for instance, that a "healthy worker effect" could explain the 2016 IRIS's lack of accuracy even though the Commission's comments had shown that not to be the case. And instead of acknowledging and correcting for the calculation error that the Commission identified, which undermined EPA's assertion that the 2016 IRIS value was more accurate than the Commission's risk assessment, the

agency just repeated explanations that the Commission had already refuted. It also offered a response that was effectively no response because it misidentified the relevant test of model validity.

II. EPA also erred in selecting breast cancer as an "endpoint" (that is, a health effect used to indicate whether a chemical is toxic) without regard to "parity bias" resulting from a failure to account for the number of children a woman has. In short, having children reduces a woman's risk of breast cancer, but working women are less likely to have children. Because the studies EPA relied on encompassed only working women, breast cancer might be more prevalent in the studied group for a reason other than exposure to ethylene oxide. Although the Commission highlighted it, EPA did not adequately account for that important aspect of the problem.

STANDARD OF REVIEW

The APA instructs courts to "hold unlawful and set aside agency action" that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *see* 42 U.S.C. § 7607(d)(9)(A) (Clean Air Act provision authorizing courts to "reverse" EPA actions on the same basis). "The APA's arbitrary-and-capricious standard requires that agency action be reasonable and reasonably explained." *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021). An administrative rule is arbitrary or capricious if the agency that promulgated it "entirely failed to consider an important aspect of the problem" or "offered an explanation for its decision that runs counter to the evidence before the agency." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

Further, "[a]n agency must consider and respond to significant comments received during the period for public comment." *Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92, 96 (2015). A comment is "significant" when it "raise[s] points relevant to the agency's decision" and "cast[s] doubt on the reasonableness of a position taken by the agency." *Home Box Off., Inc. v. FCC*, 567 F.2d 9, 35 n.58 (D.C. Cir. 1977) (per curiam). An agency's failure to respond is subject to judicial review under the "arbitrary-and-capricious standard." *Sherley v. Sebelius*, 689 F.3d 776, 784 (D.C. Cir. 2012).

ARGUMENT

I. EPA's Reliance on the 2016 IRIS Value, Instead of the Commission's Risk Assessment, Was Arbitrary and Capricious.

In the Reconsideration Decision, EPA determined that the 2016 IRIS value "represents the best inhalation cancer risk value for ethylene oxide" and that the Commission's risk assessment "is unsuitable for use as an alternative." 87 Fed. Reg. at 77,991 (JA 4104). That determination is contrary to the evidence before the agency.

During the comment period, the Commission presented two separate indicators of the accuracy of its Cox regression model and EPA's spline model. The first of those indicators, an assessment of a model's ability to accurately predict cancer deaths verifiable in the raw data, demonstrated that the Commission's risk assessment is more accurate than EPA's. The second indicator, a calculation of how accurately a model depicts the actual data, reflected a wash between the two models after accounting for a problem with EPA's numbers that the Commission identified.

In other words, the only conclusive test of the models' accuracy supported choosing the Commission's risk assessment over the 2016 IRIS value. Yet EPA arbitrarily and capriciously stuck with the 2016 IRIS value.

A. The most reliable indicator of model accuracy supports choosing the Commission's risk assessment over the 2016 IRIS value.

1. The Commission's recent, peer-reviewed risk assessment accurately predicts the cancer risk of ethylene-oxide exposure.

One way to evaluate a model's accuracy is to test whether the model can predict an outcome observed in the raw data. *See* AR-0303, Attachment A at 41, 92 (JA 3691, 3742); Food and Agriculture Organization of the United Nations World Health Organization, Hazard Characterization for Pathogens in Food and Water 41-42 (2003), https://www.who.int/publications/i/item/9241562374. The Commission did that with the 2016 IRIS. It used that model's predicted risk level, which is normally the output, as an input to see if the model would accurately estimate the number of cancer deaths recorded in the Institute's data. AR-0303, Attachment A at 42 (JA 3692).

When it did that, the Commission discovered a serious discrepancy. The 2016 IRIS predicted that, in a sample of the same size as the sample compiled by the Institute, between 92 to 141 people would die from lymphoid cancer caused by ethylene-oxide exposure. *Id.* Yet there were only 53 reported deaths in the Institute's data. *Id.* And when the Commission broke the data into five groups based on level of ethylene-oxide exposure, it found that the 2016 IRIS predicted more deaths than were actually observed in three of the four groups that were exposed to ethylene

oxide. *Id.* at 43 (JA 3693). (The remaining group was a control group comprised of people who were not exposed to ethylene oxide. *Id.* at 44 n.b (JA 3694).)

The results of the same test were much different for the Commission's Cox regression model. That model predicted between 52 to 59 lymphoid-cancer deaths, again as compared to the 53 actual deaths. *Id.* at 42 (JA 3692). The Commission's model also accurately predicted the number of lymphoid cancer deaths in each of the four groups of workers who were exposed to ethylene oxide. *Id.* at 43 (JA 3693).

Those results were not one-offs. The Commission also ran the same test using a different data set compiled by a different organization (Union Carbide Corporation or "UCC") and reached similar conclusions. *See id.* at x, 103 (JA 3650, 3753). And that is not just the Commission's say-so. Before publication, the study was subjected to peer review at the University of Cincinnati's Risk Science Center, which concluded that the Commission's Cox regression model accurately predicted the level of risk. *Id.* at 11-12 (JA 3661-62).

EPA should have heeded this persuasive indication that the Commission's risk assessment was more accurate than the 2016 IRIS value. By any definition, that is an important aspect of the problem. *See State Farm*, 463 U.S. at 43. And this Court has upheld a prior EPA decision to adjust a model to align its output with actual observed results, even where use of the unadjusted model was statutorily prescribed. *Sierra Club v. EPA*, 356 F.3d 296, 304-07 (D.C. Cir. 2004). Here, it was arbitrary and capricious for EPA not to recognize the problem arising from adherence to its unrealistic model.

2. In rejecting the Commission's assessment, EPA relied on assertions that cannot be squared with the evidence.

EPA's response to this problem was "no response at all" because, instead of engaging with the Commission's findings, EPA just "doubl[ed] down on its assertion[s]." *U.S. Sugar Corp. v. EPA*, 830 F.3d 579, 629 (D.C. Cir. 2016) (per curiam). EPA presented four reasons to reject the Commission's findings, but none is supported by the evidence before the agency.

a. In the Reconsideration Decision, EPA stated that it rejected the Commission's model as "a poor fit of the data in the low exposure range." 87 Fed. Reg. at 77,993 (JA 4106). That echoed a statement EPA made during the 2020 rulemaking, and repeated in the reconsideration rulemaking, that the 2016 IRIS values are accurate "as long as they are used in the low-exposure range, as intended." AR-0327 at 86, 88 (JA 4383, 4385); *see* AR-0200 at 96 (JA 1951).

But the Commission had previously addressed that point. *See* AR-0303 at 6 (JA 3626). As already noted, the Commission tested the 2016 IRIS using several groups representing a range of ethylene-oxide exposure levels, and it found that the 2016 IRIS overpredicted the number of cancer deaths in each of those groups. AR-0303, Attachment A at 42-43 (JA 3692-93). That includes the group with the lowest exposure—which, by EPA's account, is the group for which the 2016 IRIS should be accurate. *See* AR-0327 at 88 (JA 4385). The Commission presented this evidence to EPA, but the agency just doubled down on its prior assertions notwithstanding the evidence before it. That is an invalid approach. *See U.S. Sugar Corp.*, 830 F.3d at 629.

b. EPA also asserted that the Commission's analysis "does not imply" that the 2016 IRIS would overpredict cancer deaths if the test were "applied to a different independent data set." AR-0327 at 86, 89 (JA 4383, 4386). But as already noted, the Commission ran the same test using a different data set, and the results were essentially the same. *See* AR-0303, Attachment A at 103-04 (JA 3753-54).

The Commission made that point in its comment on the Proposed Reconsideration. *See* AR-0303 at 6-7 (JA 3626-27). EPA acknowledged the comment but offered no response. *See* AR-0327 at 86-91 (JA 4383-88). And EPA failed to acknowledge that the Commission tested the 2016 IRIS results across several groups in both the Institute's and other data and found discrepancies across the board. AR-0303, Attachment A at 42-43 (JA 3692-93). The APA requires more. *See Home Box Off.*, 567 F.2d at 35-36.

c. Next, EPA argued that the Commission failed to account for the "healthy worker effect"—that is, the notion that people who are healthy enough to work, such as everyone encompassed by the Institute's data set, may have a lower cancer risk than the less-healthy average American. AR-0327 at 86-90 (JA 4383-87); *see* Reconsideration Decision, 87 Fed. Reg. at 77,993 (JA 4106). The upshot is that the number of cancer deaths observed in the Institute's data might be lower than the number of cancer deaths in a same-sized subset of the general population. *See* AR-0327 at 88-90 (JA 4385-87). This healthy-worker effect, EPA argued, explains why the 2016 IRIS predicted far more deaths caused by ethylene-oxide exposure than the number of deaths that actually occurred. *See id.* at 89-90 (JA 4386-87).

The Commission demonstrated that a healthy-worker effect does not exist in the Institute's data. *See* AR-0303, Attachment A at 101-02 (JA 3751-52). Even so, it tested to determine whether the purported effect would make the results of the 2016 IRIS any more accurate. Specifically, the Commission adjusted its calculations to suggest that the workers in the Institute's data set were slightly healthier than the national average. *Id.* at 102 (JA 3752). But even with that adjustment, the 2016 IRIS still predicted more deaths than were in fact observed. *Id.*; *see* AR-0303 at 7-8 (JA 3627-28) (pointing out that, "even assuming that there was a healthy worker effect," the results of the Commission's "accuracy analyses do not change significantly").

Although EPA went to some length in its effort to show a healthy-worker effect, AR-0327 at 89-90 (JA 4386-87), it provided only a few lines in response to the Commission's explanation that such an effect, assuming it exists, would not make the 2016 IRIS more accurate. EPA asserted that the Commission did not adjust the calculation enough to properly account for a possible healthy-worker effect, then dismissed the Commission's adjustment as having "limited value." *Id.* at 90 (JA 4387). But EPA did not explain by how much it thought the calculations should have been adjusted. *See id.*

Nor did EPA attempt to quantify a healthy-worker effect distortive enough to account for the substantial discrepancy between its predictions and the recorded cancer deaths. *See id.* The Commission's calculations demonstrated that the 2016 IRIS predicted more than twice as many cancer deaths than actually occurred. AR-0303, Attachment A at 42 (JA 3692) (explaining that EPA's model predicted between 92

to 141 cancer deaths when only 53 were observed). EPA never contested that finding. *See* AR-0327 at 89-91 (JA 4386-88). Nor did it explain how a relatively small discrepancy between cancer deaths in the Institute's data and the national average, *see id.* at 90 (JA 4387), could account for the significant discrepancy in the 2016 IRIS predictions.

d. Finally, EPA presented two objections to parallel calculations that the Commission used to check its work. In the Reconsideration Decision, EPA stated that it had identified problems with the Commission's "calculation of projected cancer rates" and "the statistical confidence intervals [that the Commission] developed for the 'predicted' numbers of cancers." 87 Fed. Reg. at 77,993 (JA 4106). In its response to comments, EPA presented those two points in a section addressing the Commission's comment that the 2016 IRIS predicted more cancer mortalities than were reflected in the raw data. AR-0327 at 86, 90-91 (JA 4383, 4387-88) (discussing comment 22 and presenting EPA's response to calculations of cancer rates and confidence intervals). But those responses critiqued the Commission's calculations in connection with a different test of model validity.

In particular, EPA was addressing the Commission's calculations for a "standardized mortality ratio" or "SMR" test. *See* AR-0303, Attachment A at 92, 100 (JA 3742, 3750). The standardized mortality ratio is a comparison of the number of recorded cancer deaths in a study (such as the Institute's study) to an estimate of the number of expected cancer deaths in a group based on factors such as age. *See* N.E. Breslow & N.E. Day, Statistical Methods in Cancer Research Volume II: The Design and Analysis of Cohort Studies 65 (1987). The Commission believes that it correctly

calculated the standardized mortality ratio of the Institute's data and that the 2016 IRIS predicted more cancer deaths than were expected. AR-0303, Attachment A at 96-97 (JA 3746-47).

But even assuming EPA is correct that the Commission made "an error in statistical methodology" when calculating the standardized mortality ratio, AR-0327 at 91 (JA 4388), its assertion is responsive only to the Commission's calculation of *expected* cancer mortalities, *see id*. EPA never responded to the Commission's calculations showing that the 2016 IRIS also predicted more cancer mortalities than were actually recorded. *See* AR-0303, Attachment A at 41-42 (JA 3691-92). The inability of the 2016 IRIS to predict results consistent with *actual* cancer mortalities is an important aspect of the problem, and the Commission's comment raising that problem required a response. *See Home Box Off.*, 567 F.2d at 35-36.

B. When properly calculated, other tests of model accuracy were inconclusive and did not support a preference for the 2016 IRIS.

1. The Commission identified a mathematical error by EPA when calculating other indicators of model accuracy.

To assess a model's accuracy, mathematicians can calculate how closely a line charted by the model follows the actual data. Based on a miscalculation, EPA made the 2016 IRIS value appear more accurate than it in fact is. The Commission pointed that out, AR-0303 at 9 (JA 3629), and EPA failed to adequately respond.

In this context, there are two types of numbers, which together are called "model-fit criteria," that indicate a model's accuracy. The first is an Akaike information criterion value ("AIC value" or, in this acronym-averse brief, "Akaike

value"); the second is a probability value, or "p-value." *See, e.g.*, AR-0303, Attachment A at 39-40 (JA 3689-90).

The Akaike value indicates how well a model fits the underlying data. *See* Reconsideration Decision, 87 Fed. Reg. at 77,993 n.25 (JA 4106); *see also* Stéphanie Portet, A Primer on Model Selection Using the Akaike Information Criterion, 5 Infectious Disease Modelling 111, 126-27 (2020). The p-value is an estimate of the probability that a pattern found in a mathematical model could occur by chance. *See* Porta, *supra,* at 231. The lower the probability that the pattern is random, the more likely it is to be accurate. *See id.*

Calculating a model's Akaike value and p-value requires counting the number of "parameters" used in the model. *See* Portet, *supra*, at 111-12; AR-0303, Attachment A at 139-41 (JA 3789-91). A "parameter" is an estimated value within the model. *See* Portet, *supra*, at 113. The Commission explained that EPA's calculation for the model-fit criteria used two parameters when there were actually three, leading to a skewed result. *See* AR-0303 at 9 (JA 3629).

Specifically, when EPA calculated the model-fit criteria in connection with the 2016 IRIS, the two parameters it identified were the slope of the line the model drew before the knot and the slope of the line the model drew after the knot. *See* AR-0303, Attachment A at 138-39 (JA 3788-89). (As explained above, a knot is the point where two segmented lines in a spline model meet. *See supra* p. 4.) Accordingly, EPA calculated the model-fit criteria using the number "2." *See* AR-0303, Attachment A at 139 (JA 3789).

The Commission, however, identified a third parameter: the value of the knot itself. *Id.* As already noted, mathematicians determine that value in one of two ways: by either "fixing" it or "estimating [it] from the data." AR-0258 at 12 (JA 3324); *see supra* p. 3. EPA used the second method. *See* AR-0303, Attachment A at 140-41 (JA 3790-91). The result should have counted as a parameter, the Commission pointed out, because it was the product of an estimate from the data. *Id.* at 138-39 (JA 3788-89).

The Commission explained that calculating the model-fit criteria with three parameters, rather than two, mattered. It reflected that the model-fit criteria for the 2016 IRIS spline model were no better than those for the Commission's Cox regression model, so that metric provided no basis to favor the 2016 IRIS value over the Commission's assessment. *Id.* at 142 (JA 3792). That was significant because, as already noted, another indicator of model accuracy—the ability to accurately predict cancer deaths—supported choosing the Commission's risk assessment over the 2016 IRIS value. *See supra* Part I.A. As explained below, EPA's efforts to account for that problem were all deficient.

2. None of EPA's explanations for the error that the Commission identified is supported by the record.

a. EPA first tried to justify its decision to not count the knot value as a third parameter by claiming that the value was immaterial. Specifically, EPA responded to the Commission's comment by quoting a suggestion by the Science Advisory Board that "the most informative analysis will rely upon fixing some parameters rather than estimating them from the data." AR-0327 at 59 (JA 4356). EPA appeared to be

saying that, had it fixed the knot (as the Board sometimes recommends), the knot would not have counted as a parameter. *See id.* But EPA did *not* fix the knot. It chose the second method just noted, estimating the location of the knot after testing multiple options. *See* AR-0303, Attachment A at 138-39 (JA 3788-89).

The Commission identified this error in its comment on reconsideration, explaining that "[b]ecause EPA did not fix any of the parameters, the quote from the [Board] discussing the use of fixed parameters does not apply." AR-0303 at 10 (JA 3630). EPA's response just repeated the Board's statement without acknowledging the Commission's observation that it was nonresponsive. AR-0327 at 59 (JA 4356). So once again, EPA just "doubl[ed] down on its assertion" and failed to engage with the Commission's criticism. *U.S. Sugar Corp.*, 830 F.3d at 629. Such a response is "no response at all" and therefore violates the APA. *Id.*; *see id.* at 606.

b. EPA next claimed that the Board reviewed the calculation even though EPA never flagged this specific issue for it. In its response to comments, EPA stated that it took a "two-step approach" to selecting the lines and knot in its model and that the approach "was clearly presented in the draft IRIS assessment materials reviewed by the [Board]." AR-0327 at 59 (JA 4356). EPA noted that it had asked the Board to comment on "whether the method used to identify knots . . . is transparently described and scientifically appropriate." *Id.* at 60 (JA 4357). And EPA reported the Board's response as: "The method used to identify the knots . . . is scientifically appropriate and a practical solution that is transparently described." *Id.*

EPA may reasonably rely on pertinent input from the Board. But here, the Board's input was irrelevant to the Commission's criticism. As the Commission

acknowledged in its comment, the Board approved the *method* for calculating the knot and lines in EPA's model. AR-0303 at 10 (JA 3630). The excerpts EPA quoted confirm that the only question posed to the Board concerned methods of calculation. *See* AR-0327 at 59-60 (JA 4356-57). The Commission does not disagree, and has never disagreed, with EPA's chosen calculation method. *See* AR-0303 at 10 (JA 3630). Rather, the Commission disagreed with how many parameters, once calculated through a correct method, should be counted in the mathematical equation to determine model fit. *See id.*

Once again, the Commission directly commented on this concern. *Id.* EPA's decision to respond with an inapposite quotation from the Board confirms the agency's failure to "consider[] the relevant factors" or offer "a discernable path to which the court may defer." *Am. Radio Relay League, Inc. v. FCC*, 524 F.3d 227, 241 (D.C. Cir. 2008) (citing *State Farm*, 463 U.S. at 42-43).

c. EPA next asserted that the Akaike value was not an important factor. In the Reconsideration Decision, EPA repeated a prior claim that it had "followed the [Board]'s recommendations for model selection" by choosing a spline model that, among other things, "relies less on [Akaike value] and includes consideration of biological plausibility." 87 Fed. Reg. at 77,993 (JA 4106) (footnote omitted).

But as the Commission had already explained, "EPA *did* use [Akaike value] scores for model selection, as discussed in its decision not to use [other kinds of] models." AR-0303 at 12 (JA 3632) (emphasis added). In response to that comment, EPA just repeated its statement that an accurate Akaike value "would not have led to different model selection decisions in favor of the model" that the Commission

identified as accurate. AR-0327 at 60 (JA 4357). Yet EPA acknowledged that the Commission's method for calculating model-fit criteria "would lead to some increase in the calculated fit statistic ([Akaike]) and model p-values." *Id.*

It was unlawful for EPA to brush aside concerns about its flawed calculations after the Commission had shown that: (1) properly calculated model-fit criteria do not support a preference for the 2016 IRIS spline model, *see* AR-0303, Attachment A at 139 (JA 3789); and (2) EPA considered the Akaike value as a reason to select its preferred model, AR-0303 at 11-12 (JA 3631-32). Repeating debunked claims that EPA did not consider the Akaike value when selecting its model hardly constitutes reasoned decision-making.

II. EPA Arbitrarily and Capriciously Failed to Account for Parity Bias When Selecting Breast Cancer as an Endpoint.

Unlike EPA, the Commission found the relevant scientific research insufficient to support inclusion of breast cancer as an "endpoint" within its model. *Compare* Reconsideration Decision, 87 Fed. Reg. at 77,991 (JA 4104), *with* AR-0303 at 14-18 (JA 3634-38). (An "endpoint" is a health effect that may be caused by exposure to a chemical. *See, e.g.*, Elaine M. Faustman, Casarett & Doull's Toxicology: The Basic Science of Poisons, Chapter 4: Risk Assessment (9th ed. 2023 update).) The Commission's critique focused on the problem of "parity bias," an important aspect of the problem that EPA inadequately addressed.

In this context, "parity" refers to the number of times a woman gives birth. A study affected by parity bias might erroneously show that exposure to a chemical increases the risk of breast cancer when, in fact, low childbirth rates were to blame.

See Sarah M. Lima, et al., Trends in Parity and Breast Cancer Incidence in US Women Younger Than 40 Years From 1935 to 2015, AMA Network Open 2, Mar. 13, 2020. Studying breast cancer in a group comprised entirely of workers, such as the Institute's data set, allows for such bias. On average, the more children a woman has, the less time she spends in the workforce. *See* AR-0303, Attachment A at 26 (JA 3676). And as EPA acknowledged, "[t]here is substantial evidence that women who do not bear children have increased risks of breast cancer." AR-0327 at 39 (JA 4336). So it is possible that, regardless of their exposure to ethylene oxide, the female workers in the Institute's data set were already more likely than the average woman to develop breast cancer.

The Commission highlighted this problem in its comments on the Reconsideration Decision. AR-0303 at 17-18 (JA 3637-38). Specifically, it noted that two studies EPA relied on did not explain how, if at all, they accounted for parity bias. *Id.* at 18 (JA 3638). The Commission explained that it was not clear how the first study, by Steenland *et al.*, dealt with the problem, *id.* at 17-18 (JA 3637-38), and that the second study, by Mikoczy *et al.*, "did not appear to control for parity at all." *Id.* at 18 (JA 3638).

EPA acknowledged this problem, AR-0327 at 39 (JA 4336), but failed to address it. As to the Steenland study, EPA responded by stating what the study *did not* do without ever explaining how the study accounted for parity bias. In EPA's words, "Steenland et al (2003) did not indicate that parity was modeled as a time dependent variable, and that hence its inclusion in the model seems straightforward and sufficiently clear." *Id.* And as for the Mikoczy study, EPA never explained how that

study dealt with the problem. Indeed, EPA did not mention the Mikoczy study when discussing parity bias. *See id.*

EPA's inability to articulate why the results of the Mikoczy study are not flawed is a problem for the agency. Although EPA relied on other studies in addition to Mikoczy, *see* AR-0327 at 30 (JA 4327) (identifying two Steenland studies as supporting its inclusion of breast cancer as an endpoint), EPA also decided that it was "appropriate to include" the Mikoczy study "in evaluating the weight of evidence for [ethylene oxide] induced breast cancer." *Id.* at 38 (JA 4335). It is unlawful for EPA to include a study in its analysis when a commentor pointed out that the study failed to account for an important aspect of the problem that EPA itself acknowledged. *See State Farm*, 463 U.S. at 43; AR-0327 at 39 (JA 4336).

Conclusion

The Court should set aside or reverse the Rule and the Reconsideration Decision.

Respectfully submitted.

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Certificate of Service

On January 12, 2024, this brief was served via CM/ECF on all registered counsel.

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Certificate of Compliance

This brief complies with Federal Rules of Appellate Procedure 32(a)(5) and (6) because it is written in 14-point Equity typeface. It complies with Federal Rules of Appellate Procedure 29(a)(5) and 32(f) and (g) because it contains 5,835 words, excluding exempted text, according to Microsoft Word.

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