NOT YET SCHEDULED FOR ORAL ARGUMENT

No. 23-1085 and consolidated cases

U.S. COURT OF APPEALS FOR THE DISTRICT OF COLUMBIA CIRCUIT

Huntsman Petrochemical LLC, American Chemistry Council,
and Louisiana Chemical Association,
Petitioners,

v.

U.S. Environmental Protection Agency,
Respondent.

Petition for Review of Rules of
the U.S. Environmental Protection Agency

EPA's Proof Answering Brief

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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

As required by D.C. Circuit Rule 28(a)(1), EPA certifies:

A. Parties and amici

Other than the Union of Concerned Scientists, an intervenor for EPA, all parties appearing here are listed in Petitioners' opening brief.

Amici for Petitioners are: Chamber of Commerce of the United States of America, Ethylene Oxide Sterilization Association, National Association of Manufacturers, Sterigenics U.S., LLC, and Texas Commission on Environmental Quality.

B. Rulings under review

Under review are two EPA actions:

- National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review, 85 Fed. Reg. 49,084 (Aug. 12, 2020), as it relates to issues severed from Case Nos. 20-1414 and 20-1418. *See Huntsman Petrochemical LLC v. EPA*, Case No. 20-1414 and consolidated cases, Order (Mar. 28, 2023).
- Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical

Manufacturing Residual Risk and Technology Review, 87 Fed. Reg. 77,985 (Dec. 21, 2022).

C. Related cases

Huntsman Petrochemical LLC v. EPA, Case No. 20-1414 and consolidated cases (D.C. Cir.), challenges the 2020 action.

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

*Authorities upon which we chiefly rely are marked with asterisks.

Statutes

Code of Federal Regulations

Federal Registers

GLOSSARY

2014 Eval Draft	EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Aug. 2014)
2020 Resp. to Comments	Summary of Public Comments and Responses for the Risk and Technology Review for Miscellaneous Organic Chemical Manufacturing (May 2020)
Br.	Brief of Petitioners
EPA	U.S. Environmental Protection Agency
EtO Eval	EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Dec. 2016).
JA	Joint Appendix
Model Memo	Sensitivity of Ethylene Oxide Risk Estimates to Dose-Response Model Selection (Oct. 2019)
Resp. to Comments	Summary of Public Comments and Responses for the Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review (Dec. 2022)
Resp. to ACC Req.	Response to Request for Correction from American Chemistry Council (Aug. 2021)
Texas Eval	Texas Commission on Environmental Quality, Ethylene Oxide Carcinogenic Dose-Response Assessment (May 2020)

INTRODUCTION

This dispute arises from EPA's efforts to regulate emissions of ethylene oxide, a human carcinogen.

In 2016, EPA calculated the cancer risk of ethylene oxide, a toxic gas that Congress deemed a hazardous air pollutant under the Clean Air Act. Using that cancer-risk estimate, EPA determined that certain ethylene-oxide emissions posed unacceptable risk to public health. So it tightened regulations of those emissions.

The calculation of the cancer-risk estimate called on EPA's expertise in statistics and toxicology. And EPA made sure that its conclusions reflect the voluminous epidemiological data it had gathered. The resulting estimate is the sort of fiendishly complicated technical decision to which the Court gives the greatest deference.

Enter Petitioners, chemical manufacturers that emit ethylene oxide. They think EPA's cancer-risk estimate is too high. So they invite the Court to play both statistician and toxicologist, offering hyper-technical critiques of the statistical model that EPA developed to capture the relationship between ethylene-oxide exposure and cancer risk.

The Court should reject that invitation. EPA's estimate is scientifically and analytically sound. It is Petitioners who err—by misunderstanding statistical methods and EPA's analysis, by overreading unvalidated and poorly executed

studies, by ignoring the data itself. The Court should defer to EPA's evaluation of scientific data within its area of expertise and deny the petitions.

STATEMENT OF JURISDICTION

The Court has jurisdiction under 42 U.S.C. § 7607(b)(1).

ISSUES PRESENTED

The Clean Air Act directs EPA to set emission standards if it determines that emissions from a regulated source category continue to pose unacceptable risk to public health. 42 U.S.C. § 7412(f)(2). EPA made that determination for the Miscellaneous Organic Chemical Manufacturing source category. In doing so EPA used its cancer-risk estimate for ethylene oxide. The issues presented are:

1. To estimate ethylene oxide's cancer risk, EPA relied on high-quality epidemiological data of workers exposed to the chemical. At the same time, it rejected irrelevant data and data from unvalidated and poorly executed studies. Did EPA act reasonably?
2. In calculating cancer risk, EPA used a dose-response model that describes the relationship between ethylene-oxide exposure and cancer risk. The agency developed the model using sound statistical methods, while rejecting unrealistic alternatives. Should the Court uphold EPA's use of its model here?

3. EPA invited external peer reviewers, other agencies, and the public to comment—multiple times—on the calculation and use of its cancer-risk estimate. The agency then responded substantively to the comments. Are EPA's actions procedurally sound?
4. The Clean Air Act's mandatory exhaustion rule, 42 U.S.C. § 7607(d)(7)(B), limits judicial review to issues that were raised with reasonable specificity in the rulemaking. Petitioners concede that in the rulemaking, they failed to argue that Congress improperly delegated authority under Section 7412(f)(2). Can the Court consider that argument?

STATUTES AND REGULATIONS

Pertinent statutes and regulations are in the addendum to this brief.

STATEMENT OF THE CASE

I. The uses and dangers of ethylene oxide.

Ethylene oxide, a gas at room temperature, is often used to sterilize medical equipment and fumigate spices.[1] EtO Eval 2-1, JA____. But the quality that makes ethylene oxide an effective sterilant—the ability to kill microorganisms—is also what makes it toxic. Indeed, ethylene oxide has long been known to damage chromosomes in organisms from bacteriophage to humans. *Id.* 1-1, 3-1, JA____,

[1] Ethylene oxide is also used to produce ethylene glycol, an industrial chemical used in many consumer products. EtO Eval 2-1, JA____.

____. In 1990, Congress listed ethylene oxide as a hazardous air pollutant to be regulated under the Clean Air Act. 42 U.S.C. § 7412(b)(1); Pub. L. No. 101-549, § 301, 104 Stat. 2399, 2534 (1990).

Because ethylene oxide is normally a gas, inhalation is the main exposure route. Human exposure often occurs on the job, through contact with the gas in chemical factories and sterilization facilities. EtO Eval 2-1, JA____. People living nearby can also breathe in the toxic gas. *Id.*

EPA first evaluated ethylene oxide's toxicity in 1985. *Id.* 3-1, JA____. Since then, new studies have shown the chemical to be much more toxic than EPA had thought. *See id.* App. A, JA____-__. In 1998 EPA, through its Integrated Risk Information System, began to update its ethylene-oxide evaluation.[2]

The System is run by EPA's Office of Research and Development to identify and characterize the health hazards of chemicals around us. These toxicologic evaluations are rigorous: They are based on science. They examine relevant studies by academics, government agencies, and industry. And they undergo not only review by EPA and the public, but also external peer review. *See* Resp. to Comments 16-18, JA____-__.

[2] EPA, Evaluation of the Carcinogenicity of Ethylene Oxide (2006 External Review Draft), *available at* https://perma.cc/7FHS-9TXC ("History" tab). The Integrated Risk Information System is commonly known as IRIS and referred to as such in the record. The record also uses "IRIS value" or "URE" (unit risk estimate) to describe EPA's cancer-risk estimate.

II. EPA estimates ethylene oxide's cancer risk

Eighteen years in the making, EPA's updated ethylene-oxide evaluation required extensive efforts. During this time, EPA reviewed many epidemiological studies of ethylene oxide's toxicity in humans. EtO Eval 3-1 to 19, JA____-__ (noting that EPA scrutinized the studies' design, exposure assessment, data analysis, and more).

EPA's review found "strong evidence" that ethylene-oxide exposure increases cancer risk. *Id.* 1-1, 3-6 to 13, JA____, ____-__. A key piece of evidence came from a high-quality, large-scale study by the National Institute for Occupational Safety and Health, which found that exposed sterilizer workers face higher risks of lymphoid cancer[3] and breast cancer. *Id.* 1-1, JA____. And though human studies like the Institute's showed "strong, but less than conclusive on its own," evidence of those cancers, other studies showed "extensive evidence" of carcinogenicity in lab animals, including lymphohematopoietic cancers and mammary carcinomas in exposed rodents. *Id.*; *see id.* 3-20 to 23, JA____-__. There was also clear evidence that ethylene oxide damages DNA. *Id.* 1-1 to 2, JA____-__. Based on the weight of the evidence, EPA concluded that ethylene oxide, when inhaled, is a human carcinogen. *See id.* 1-1, JA____ (noting that EPA

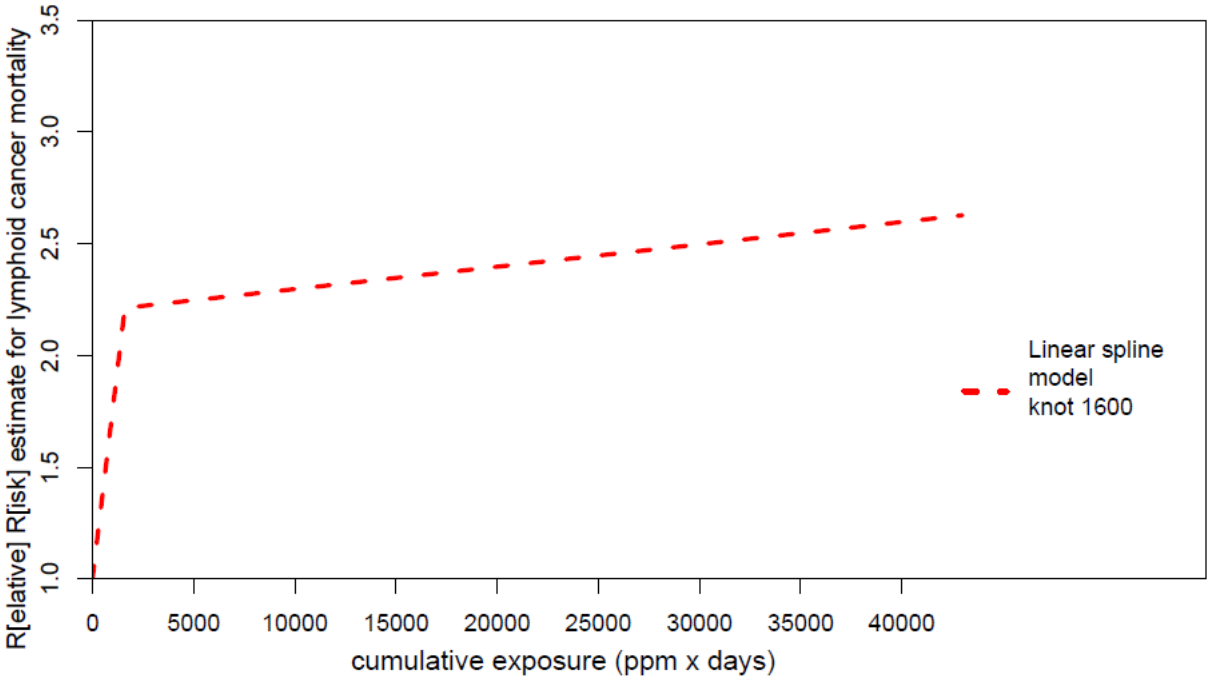
[3] Lymphoid cancer, a subset of lymphohematopoietic cancers, includes non-Hodgkin's lymphoma, myeloma, and lymphocytic leukemia. EtO Eval 4-6, JA____.

followed its guidance for carcinogen risk assessment, available at JA____-__), 1-7, JA____ (summarizing major findings).

Next, using the Institute's study, EPA estimated ethylene oxide's additional lifetime cancer risk at 5.0×10^{-3} per $\mu g/m^3$. *Id.* 1-2, 4-91, JA____, ____. This means that a lifetime exposure to 1 microgram of ethylene oxide per cubic meter of air increases cancer risk by 5 in 1000 people, or 0.5%. And it is about 60 times higher than EPA's earlier estimate, which was based only on animal data. 84 Fed. Reg. 69,182, 69,217/2 (Dec. 17, 2019). Note that the cancer-risk estimate is the incremental risk from exposure *above* any preexisting exposures, such as from background ethylene-oxide levels. Resp. to ACC Req. 6, JA____.

EPA calculated cancer risk using dose-response models that show the relationship between ethylene-oxide exposure and cancer risk. In developing these models EPA followed not only its own guidelines for assessing carcinogens, but also advice from external scientific peer reviewers on the Science Advisory Board.[4] EtO Eval App. H-I, K, JA____-__, ____-__. Here is EPA's dose-response model (called a two-piece linear spline) for lymphoid cancer:

[4] Congress directed EPA to establish the Science Advisory Board to give the agency scientific advice. 42 U.S.C. § 4365. The board comprises about 50 nationally renowned scientists, engineers, and economists who are screened for conflicts of interest. Resp. to Comments 16, JA____; *see* EtO Eval xvi-xviii, JA____-__ (identifying members who reviewed the ethylene-oxide evaluation).



See id. 4-21, JA____ (Figure 4-3) (also showing other dose-response models EPA considered). EPA developed a similar dose-response model for breast cancer. *Id.* 4-50 to 52, JA____-___. Using these models, EPA estimated risks for each cancer and from them, the overall cancer risk. *Id.* 4-2, JA____.

Three things to keep in mind about EPA's evaluation. First, it revolved around environmental, not occupational, exposure. That follows from EPA's focus, under the Clean Air Act, on the public's exposure to ambient air. *See, e.g.*, 42 U.S.C. § 7412(f)(2)(A) (directing EPA to protect "public health," not occupational health).[5] The Institute's study, however, examined a range of

[5] Occupational exposure to harmful chemicals is primarily regulated by the Occupational Safety and Health Administration. 29 U.S.C. §§ 652(8), 655(b)(5). Ethylene oxide can be used as a pesticide (to sterilize or fumigate), and because

Cont.

ethylene-oxide exposures to sterilizer workers. *E.g.*, EtO Eval 1-3, 4-21, JA____, ____. The general public is unlikely to face (higher) occupational levels of exposure. Its exposure, which in particular occurs when people living near ethylene-oxide facilities breathe in emissions, tends to be lower. So EPA's risk assessment primarily focused on lower, environmental exposures. *See id.* 1-4, JA____.

Second, EPA's dose-response model describes cancer risk relative to a person's baseline cancer risk. For example, at an exposure of 1,600 ppm–days[6] (the model's "knot," where the slope changes), a person is more than twice as likely to die of lymphoid cancer compared to not having that exposure (that is, her risk is more than twice her baseline risk).

Third, the Institute's data, reflected in the model's shape, shows that at lower exposures (below the knot), each additional ethylene-oxide dose leads cancer risk to spike, while at high exposures, risk plateaus. *Id.* 4-12, JA____. That is not unusual: Many occupational carcinogens have dose-response models with the same shape. *See* 2020 Resp. to Comments 95, JA____.

EPA regulates pesticides, it also estimated cancer risk for certain occupational exposures. 7 U.S.C. §§ 136-136y; EtO Eval 2-1, 4-99 to 111, JA____, ____-__. That estimate was calculated separately from the disputed estimate, which applies to environmental exposure.

[6] "ppm–days" represents cumulative exposure, calculated using exposure concentration (in parts per million) and exposure period (in days).

* * *

EPA's ethylene-oxide evaluation, including the cancer-risk estimate, underwent two rounds of external peer review by the Science Advisory Board. EtO Eval 2-2, JA____. After each round EPA addressed the board's comments. *Id.* App. H-I, JA____-__, ____-__. The evaluation was also reviewed by over a dozen EPA programs and regional offices, as well as other federal agencies and the public. *Id.* xv, JA____; *see id.* App. H, K, JA____-__, ____-__. EPA finalized its evaluation of ethylene oxide in December 2016.

III. Using its cancer-risk estimate, EPA concludes that certain ethylene-oxide emissions pose unacceptable health risks.

EPA used its new cancer-risk estimate in a regulatory action for the first time in 2020. 85 Fed. Reg. 49,084 (Aug. 12, 2020). That was when it reviewed ethylene-oxide emission standards for the Miscellaneous Organic Chemical Manufacturing source category, made up of nearly 200 facilities. 84 Fed. Reg. at 69,189/3; *see id.* 69,184/3 (giving examples of chemicals produced at those facilities, such as polyester resins and photographic chemicals); 68 Fed. Reg. 63,852 (Nov. 10, 2003) (promulgating standards); 70 Fed. Reg. 38,554 (July 1, 2005) (amendments); 71 Fed. Reg. 40,316 (July 14, 2006) (amendments); 40 C.F.R. Part 63, subpart FFFF.

As background, the Clean Air Act regulates emissions of hazardous air pollutants (like ethylene oxide) using a two-stage process. *See* 42 U.S.C. § 7412.

First, for each category of regulated sources, EPA sets technology-based emission standards. *Id.* § 7412(d). Later, EPA reviews the standards to see (1) whether to update them given technological developments, *id.* § 7412(d)(6), and—relevant here—(2) whether more measures are needed to address any remaining health risks or adverse environmental effects, *id.* § 7412(f)(2).

The Section 7412(f)(2) review considers, among other things, the maximum lifetime individual cancer risk from exposure to the source category's emissions. EPA's formula for calculating that risk is: estimated lifetime exposure to ambient concentration x cancer-risk estimate. 84 Fed. Reg. at 69,191/1. This risk is generally presumed to be acceptable if it is no higher than 1 in 10,000 (or 100 in a million).[7] *See* 54 Fed. Reg. 38,044, 38,044/3-45/3 (Sept. 14, 1989) (setting forth EPA's approach); 42 U.S.C. § 7412(f)(2)(B); *NRDC v. EPA*, 529 F.3d 1077 (D.C. Cir. 2008).

EPA completed its Section 7412(f)(2) review of the Miscellaneous Organic Chemical Manufacturing source category in 2020. Using its updated cancer-risk estimate, EPA calculated the maximum lifetime individual cancer risk. For people living near regulated sources, that risk was as high as 400 in a million—four times what EPA normally considers acceptable. 85 Fed. Reg. at 49,095/3-96/2 & tbl. 3.

[7] That is, a 100 in a million chance of developing cancer due to a lifetime's exposure to emissions from regulated sources.

Based on this risk and other information, EPA determined that ethylene-oxide emissions from the source category posed unacceptable risk. *Id.* 49,088/3; 2020 Resp. to Comments 20, JA____. As a result, the Clean Air Act required EPA to set emission standards that reduce risk to acceptable levels and provide ample margins of safety. 85 Fed. Reg. at 49,088/3; 42 U.S.C. § 7412(f)(2)(A). Because the risk here was driven by emissions from process vents, equipment leaks, and storage tanks, as part of its Section 7412(f)(2) review EPA tightened emission standards for those sources. 85 Fed. Reg. at 49,088/3-89/2.

IV. EPA reaffirms its cancer-risk estimate.

In the 2020 rulemaking, EPA solicited comments on the use of its cancer-risk estimate. 84 Fed. Reg. at 69,218/2. Many commenters raised issues that had been addressed during peer and public reviews of the 2016 evaluation. 85 Fed. Reg. at 49,097/3.

One commenter was Texas's environmental agency, which had recently proposed its own cancer-risk estimate for ethylene oxide. *Id.* 49,098/2. But because Texas's estimate had not been finalized or even peer reviewed by the close of EPA's comment period, EPA did not consider it in the 2020 rulemaking. *See id.* & n.12 (noting that Texas finalized its estimate in May 2020, over three months after the comment period closed).

Soon after EPA finalized the 2020 rule, Petitioners sought administrative reconsideration. EPA agreed to reconsider—and invited public comment on—two issues: (1) use of EPA's cancer-risk estimate in the 2020 rule, and (2) use of Texas's estimate as an alternative. 87 Fed. Reg. 6,466, 6,467/1 (Feb. 4, 2022).

Texas's cancer-risk estimate is some 3,000 times lower than EPA's. *See* Texas Eval 58, JA____. Two things largely explain that difference. First, Texas excluded breast-cancer risks from its calculation. 87 Fed. Reg. 77,985, 77,991/2 (Dec. 21, 2022). Second, Texas's dose-response model is unsupported by epidemiological data and relies on erroneous analysis. *Id.* 77,991/2-3. These problems, EPA said, made Texas's estimate unsuitable for use. *Id.* 77,991/2; *see* Resp. to Comments 18-41, 44-91, JA____-__, ____-__.

In its reconsideration EPA once again responded to public comments, many of which had been made—and addressed—in both the 2016 evaluation and the 2020 rulemaking. 87 Fed. Reg. at 77,990/1-2. Because nothing in the comments called its cancer-risk estimate into question, EPA decided against changing the 2020 rule, finalizing that decision in December 2022. *Id.* 77,991/1, 77,986/1.

V. Procedural history.

Two of the Petitioners, along with Intervenors, challenged the 2020 rule. *Huntsman Petrochemical LLC v. EPA*, Case No. 20-1414 and consolidated cases (D.C. Cir.). Those cases were put into abeyance pending reconsideration. *See*

EPA's Unopposed Mot. to Govern, Case No. 20-1414 and consolidated cases (Mar. 3, 2023) (summarizing procedural history). Petitioners then challenged EPA's reconsideration decision. *Huntsman Petrochemical LLC v. EPA*, Case No. 23-1045; *Am. Chemistry Council v. EPA*, Case No. 23-1047.

The Court severed the cancer-risk issues raised in the petitions challenging the 2020 rule and consolidated them with the reconsideration challenge. EPA's Unopposed Mot. to Govern, Case No. 20-1414 and consolidated cases (Mar. 3, 2023); Order (Mar. 28, 2023). The result, No. 23-1045 and consolidated cases, is now before the Court.

STANDARD OF REVIEW

This Court reviews the challenged actions under the same arbitrary-and-capricious standard as under the Administrative Procedure Act. *See* 42 U.S.C. § 7607(d)(9)(A); *Miss. Comm'n on Env't Quality v. EPA*, 790 F.3d 138, 150 (D.C. Cir. 2015) (per curiam). The Court gives an "extreme degree of deference" to EPA's evaluation of scientific data within its area of expertise, especially here, when the agency is administering complicated provisions of the Clean Air Act. *Miss. Comm'n*, 790 F.3d at 150. The question for the Court, then, is not whether it or anyone else "[l]ooking at the same data…would simply reach a different conclusion." *Id.* at 162. It is whether EPA "considered all relevant factors and articulated a rational connection between the facts found and the choice made." *Id.*

at 150 (internal quotation marks omitted). The Court will "uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned." *Catawba Cnty. v. EPA*, 571 F.3d 20, 50 (D.C. Cir. 2009) (per curiam).

Statistical analysis, in particular, "is perhaps the prime example of those areas of technical wilderness into which judicial expeditions are best limited to ascertaining the lay of the land." *Appalachian Power Co. v. EPA*, 135 F.3d 791, 802 (D.C. Cir. 1998) (per curiam). When, as here, EPA uses statistical analysis, all that the Court needs to uphold the agency's action is a "rational relationship" between the agency's statistical model and the underlying data. *Id.* The Court will not, "as nonstatisticians,…perform [its] own statistical analysis—a job more properly left to the agency to which it was delegated." *Id.*

SUMMARY OF ARGUMENT

This dispute targets EPA's statistical analysis of ethylene oxide's cancer risk. It is hard to imagine a more technical dispute, or one commanding more judicial deference. To uphold EPA's actions, the Court needs to find only a rational connection between the facts before EPA and what the agency did. That connection exists in spades.

I. EPA used high-quality epidemiological data to estimate cancer risk. This data, from the biggest and most comprehensive human study available, elicits little objection from Petitioners. Rather, when it comes to the data, they limit their

arguments to marginal issues. Those arguments rely on a mix of bad science and bad analysis, and the Court should reject them.

II. Using its high-quality data, EPA developed a dose-response model to calculate cancer risk. But the data was voluminous. So EPA used a common statistical method to organize the data and discern the dose-response relationship. This relationship, EPA's method revealed, behaves differently at different exposure levels: At low exposures, risk skyrockets with more ethylene-oxide doses; at high exposures, risk plateaus. And because EPA's evaluation focused on environmental, not occupational, exposures, the agency wanted its dose-response model to have good fit at low exposures.

EPA's model reflects these considerations: It has two distinct slopes that capture the two distinct dose-response relationships. And it fits the data well both overall and at low exposures.

None of that can be said of the model that Petitioners seem to prefer. That model makes no sense, predicting that people would face more cancer risk even without additional exposure. Perhaps the most striking critique of Petitioners' preferred model comes from its creator, Texas, which did not use it to come up with its own cancer-risk estimate. At the same time, the model that Texas *did* use bears no resemblance to the dose-response relationship or risk magnitude shown in

the Institute's data. As for Texas's attempt to check EPA's model for accuracy, it proved only that the state misapplied the model, not that the model was faulty.

III. EPA invited and responded to public comments—over and over again—on its cancer-risk estimate. Petitioners treat EPA's disagreements with their technical comments as a sign of procedural defect. The Court should reject Petitioners' attempt to dress up their substantive objections in procedural garb.

IV. Though Petitioners now contend that Congress improperly delegated authority under Section 7412(f)(2), their failure to exhaust this nondelegation argument bars the Court from considering it. In the rulemaking, Petitioners had two chances to make that argument. Yet they kept quiet, opting instead to spring it on EPA in litigation. The Court should enforce the Clean Air Act's mandatory exhaustion rule and refuse to consider the nondelegation argument. At any rate, Congress spelled out intelligible principles when delegating authority to EPA.

ARGUMENT

I. EPA used high-quality data to estimate cancer risk.

In estimating ethylene oxide's cancer risk, EPA used the Institute's study of sterilizer workers. EPA concluded this was a "high-quality" study and, of the studies it reviewed, best suited for estimating risk. EtO Eval 1-2, JA____. Many features contributed to its quality. *Id.* 1-2 n.1, JA____. To highlight a few:

First, the study was by far the largest of the available human studies, examining over 17,000 workers at 13 sterilization facilities. *Id.* 1-2, 3-6, 4-3, D-65 to 66, JA____, ____, ____, ____-__.[8] About 55 percent of those workers were women, a group often underrepresented in industrial studies. *Id.* 4-60, JA____; 87 Fed. Reg. 77,992/3.

Second, the Institute's study followed its participants for over 25 years, long enough to detect cancer. EtO Eval 3-6, 4-60, JA____, ____.

Third, the workers were exposed only to ethylene oxide and not to other occupational carcinogens found at less specialized chemical factories. *Id.* 1-2 n.1, 4-72, JA____, ____. The study thus had no known confounding exposures.[9]

Finally, the study used internal comparisons to correct for the healthy-worker effect. Workers, for various reasons, tend to have better health than the average person. *See id.* 1-2 n.1, 3-7, JA____, ____; Resp. to Comments 37, JA____ (noting that workers may differ from the general population in many ways, such as by demographics and availability of medical care), 89, JA____ (noting that the healthy-worker effect is often seen in occupational epidemiology). A direct

[8] *See* EtO Eval 3-14 to 17, JA____-__ (summarizing lymphohematopoietic-cancer studies, whose sample sizes generally fall between roughly 1,000 to 3,000 people); *see also id.* 3-18 to 19, JA____-__ (summarizing breast-cancer studies).

[9] Confounding variables are "other factors that could explain an observed association between a substance and the disease." *Hardeman v. Monsanto Co.*, 997 F.3d 941, 964 n.15 (9th Cir. 2021).

comparison between disease rates in workers and in the general population would ignore this effect. *See* Resp. to Comments 37, JA____.

Internal comparison helps fix this problem. The comparison entails identifying a group of unexposed workers (think of it as a "control" group of sorts) and comparing it with exposed workers. The difference in cancer risk between these groups—untainted by any factors that distinguish workers from everyone else—is attributable to the exposure itself. *See id.* 37, 89-90, JA____, ____-__; EtO Eval 3-7, JA____.

Petitioners do not criticize the overall quality of the Institute's data. *Cf.* Texas Eval 29-32, JA____-__ (noting that Texas also used that data).[10] Rather, their attacks aim for the margins: (A) endogenous and background levels, which were made irrelevant by internal comparisons; (B) smoking studies that observed effects of a witches' brew of chemicals, not effects of ethylene oxide alone; and (C) pre-1978 occupational exposures. Br. at 30-38, 52-53. Those attacks all miss their marks.

[10] As Petitioners note, EPA lacked data at the lowest exposures, which are beyond current measuring capabilities. Br. 9, 41. That means that Texas also lacked that data. So both had to extrapolate at the lowest exposures. To the extent that Petitioners dispute EPA's extrapolation (and this is unclear), they appear to do so by challenging pre-1978 exposure estimates and EPA's choice of dose-response model. *See id.* 31, 41; *infra* Argument §§ I.C, II.

A. Endogenous and background levels did not affect EPA's cancer-risk estimate.

Petitioners' first miss involves endogenous and background ethylene-oxide levels. Br. 33-35. This argument barks up the wrong tree.

That is because EPA estimated the increased cancer risk due to additional exposure *above* any risk from endogenous or background levels. EtO Eval K-9, JA____; Resp. to ACC Req. 6, JA____. So those levels did not, as Petitioners urge, affect EPA's estimate. Or, put another way, whatever the endogenous and background levels are, Br. 33, all sterilizer workers in the Institute's study would have been exposed to them. Resp. to Comments 64, JA____. Any effects from those exposures (including baseline cancer risks) would have been zeroed out in the internal comparison, which isolated health effects from *differences* in worker exposures. *See* EtO Eval 4-95, JA____ (noting that baseline lymphoid-cancer risk is 3 percent). Endogenous and background levels, then, could not have played a role in EPA's analysis.

Petitioners lob a slew of endogenous and background numbers (in different units—parts per trillion—from what is in EPA's analysis), hoping that some will stick, or at least sow confusion. Br. 33-34. Start with endogenous levels. *Id.* 34. Petitioners rely on a study funded by one of them, American Chemistry Council. Resp. to Comments 66, JA____. The study reviews other studies that "provide little quantitative data on levels of endogenous [ethylene oxide] that may actually

be produced in humans." *Id.* The study also makes "highly speculative" inferences and offers only "exploratory and qualitative findings." *Id.* Just as EPA reasonably rejected the study, so should the Court reject Petitioners' argument relying on that study.

Nor do the background levels Petitioners offer undermine EPA's cancer-risk estimate. Br. 33. To begin, monitoring data of ambient background levels is uncertain. Resp. to Comments 69-70, JA____-__. One reason is that some background levels are too low for monitors to reliably measure. *See id.* (noting that monitoring sometimes shows ethylene oxide at levels "close to the detection limit").[11] It is thus impossible to state background levels with confidence. *See id.* Without any citation of the record, Petitioners refer to "readings that overstate [ethylene-oxide] background levels by *two orders of magnitude*." Br. 35. Setting aside that it is unclear what numbers they are comparing, the point is that, as EPA

[11] By contrast, EPA has high confidence in data from monitors immediately downwind of ethylene-oxide facilities, where ethylene-oxide levels are higher. Resp. to Comments 69, JA____; *see* Br. 34.
The uncertainty plaguing ambient monitoring data is also why EPA's Section 7412(f)(2) review did not use that data to calculate maximum lifetime cancer risk. Br. 20, 34-35. It used *modeled* ambient levels, and the modeling looked only at emissions from the source category, not background levels. *See* 84 Fed. Reg. at 69,190/3-91/1.

explained, there is little reason to be confident in the background monitoring data. So any sort of comparison to background levels—like Petitioners'—is unreliable.[12]

Petitioners also brandish a "0.1 ppt 1-in-1,000,000 level for risks above background." Br. 33; *see id.* 30 (mentioning the "IRIS Value's 1-in-1,000,000 risk value."). Candidly, we do not know what they mean, and still less what role this figure plays in their argument. *See id.* 33-35. To be clear, EPA's cancer-risk estimate—the risk at issue—is 5.0×10^{-3} per $\mu g/m^3$, not 1 in a million. *See supra* Statement of the Case § II. Nor did EPA require risk reduction down to 1 in a million. *See* 85 Fed. Reg. at 49,096/1, 49,102/1 (noting that post-control cancer risk is 200 in a million). Petitioners' "level for risk above background" is thus irrelevant to EPA's risk analysis.

More importantly, for all their endogenous and background talk, Petitioners do not challenge the actual statistical analysis that EPA relied on and that separated

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[12] To put Petitioners' background levels into perspective, consider 150 ppt, about the average of the levels offered. Br. 33. Because EPA's dose-response model is based on ppm–days for workers, we need to convert 150 ppt into that unit. That entails converting a continuous environmental exposure into occupational exposure. *See* EtO Eval E-3, JA____ (column K) (conversion factors). The result: 150 ppt is equal to about 11.65 ppm–days.* In contrast, the low exposures that EPA focused on in deriving its model extend from 0 to 1,600 ppm–days. *See supra* Statement of the Case § II.

*Here is the math: 150 ppt = 0.00015 ppm→

$$0.00015 \text{ ppm} \times 365 \text{ days per year} \times 70 \text{ years} \times \left(\frac{365}{240} \times \frac{20}{10}\right) = 11.65 \text{ ppm–days}$$

endogenous and background levels from the exposures at issue. Granted, high endogenous and background levels could theoretically make it harder to observe risks from additional exposures. EtO Eval 4-94, JA____. But through internal comparisons, the Institute's study quantified workers' additional exposures—exposures above endogenous and background levels—as well as those workers' excess cancer risks. Petitioners do not challenge those results in arguing about endogenous and background levels. The Court should thus reject those arguments.

B. EPA reasonably rejected smoking studies marred by confounding exposures and unvalidated assumptions.

Petitioners' smoking studies do not undercut EPA's cancer-risk estimate. Those studies, Petitioners say, show that although cigarette smoke supposedly exposes smokers to enormous amounts of ethylene oxide, smoking is not causally linked to lymphoid cancer. Br. 31-32, 52. But Petitioners overread the studies (again funded by Petitioner American Chemistry Council) in two ways. Resp. to Comments 18, JA____.

First, cigarette smoke contains lots of chemicals, many of them carcinogens. *Id.* 68-69, JA____-__. Those chemicals can interact with each other in complex ways to cause lots of cancers, which may or may not include lymphoid cancer. The smoking studies, which do not address these interactions, thus say nothing about the effects of one of the chemicals—ethylene oxide—standing alone. *See id.* And they cast no shade on the Institute's study, which did examine ethylene oxide

without a chemical stew of confounding exposures and showed that ethylene oxide causes lymphoid cancer. Br. 32.

Even if the smoking studies could legitimately show ethylene oxide's relationship (or lack thereof) with lymphoid cancer, there would still need to be a quantitative analysis of that relationship. Resp. to Comments 68-69, JA____-__. Otherwise, there would be no way to know how the studies' observed lymphoid-cancer rate compares with non-smokers' rate. Petitioners, however, offer no such quantitative analysis. *Id.* 69, JA____.

Second, the smoking studies used an unvalidated method to measure exposure. *Id.* 31, 68-69, JA____, ____-__. Rather than directly measure ethylene-oxide exposure from cigarette smoke, the studies estimated exposure using a hemoglobin biomarker (called hydroxyethylvaline adducts) as a proxy for ethylene-oxide levels in blood. But the biomarker, though useful as such in workers with high occupational exposures, is not validated to assess the lower environmental exposures faced by the general population. *Id.* 31, 65-69, JA____-__; *see* Am. Chemistry Council, Comment (Mar. 19, 2020) at 18 & n.39, JA____. Further clouding this biomarker's role as a proxy, smoking causes physiological and biochemical changes that could affect smokers' ethylene-oxide exposures and formation of the biomarker. Resp. to Comments 69, JA____.

In sum, because the smoking studies did not adequately control for confounding exposures or even reliably measure exposure, EPA reasonably rejected them.

C. EPA used reasonably estimated pre-1978 exposure levels.

Petitioners also criticize how the Institute's study estimated pre-1978 exposures. Br. 36-38. That criticism is both muddled and misplaced.

To begin, the Institute had extensive data from the late 1970s and onward to assess worker exposure in detail. EtO Eval 4-64, JA____. A complex model to estimate exposure levels was developed using the data. *Id.*; *see id.* 4-64, JA____ (noting that the model accounted for 85 percent of variations in exposure in an independent set of test data); *id.* A-14 to 16, JA____-__. Two of the variables that went into the exposure model as inputs were calendar year and the volume of sterilization chambers at each facility. *Id.* 4-64 to 65, JA____-__.

For later periods in the analysis, calendar year was used as a surrogate for improved workplace protections that reduced exposure. *Id.* 4-64, JA____; *see id.* 4-65, JA____ ("This variable captured decreases in exposure after the late 1970s that were unaccounted for by the other variables."); 2014 Eval Draft H-8 to 9, JA____-__. But people began to worry about ethylene oxide's toxicity only starting in the late 1970s. EtO Eval 4-65, JA____. For the period before that, there was little reason to think that factories took special steps to shield workers

from exposure, and thus little reason to use calendar year as a surrogate for those protective steps. *See id.* I-26 to 27, 4-64 to 65, JA____-__, ____-__; Resp. to ACC Req. 2-3, JA____-__; *cf.* EtO Eval I-26 to 27, JA____-__ ("increased controls were used after it became known that [ethylene oxide] might be dangerous.").

The Institute thus omitted calendar year as a variable when estimating pre-1978 exposures. *See* EtO Eval 4-65, JA____. It instead relied primarily on each plant's sterilization-chamber volume: The bigger those chambers, the greater the worker's exposure. *Id.* 4-65, JA____; *see id.* 3-6, JA____. Of course, given the absence of reliable exposure-related data from that earlier period, it was impossible to prove the assumed relationship between exposure level and sterilization-chamber volume. *Id.* 4-64 to 65, JA____-__. But EPA articulated a rational connection between the facts and its choices. *See Miss. Comm'n*, 790 F.3d at 150.

To be sure, during peer review, the Science Advisory Board expressed "surpris[e]" that two plants had lower exposure estimates before 1975. EtO Eval I-26, JA____; Br. 36. But those estimates, EPA explained, were based on sterilization-chamber volume, which increased as demand for sterilized products increased. EtO Eval I-26, JA____. That was true at the two plants in question. *Id.* I-26 to 27, JA____-__; *see* Resp. to ACC Req. 3, JA____. So the exposure patterns flagged by the board were not anomalous; they simply reflected

underlying demand for sterilized products. There was nothing arbitrary about the pre-1978 exposure estimates.

Petitioners' argument is, at best, muddled. They first criticize the assumption that "workers were exposed to *less* [ethylene oxide] *before* 1978 than after." Br. 36. But in the next breath they cite evidence of "specific changes in work practices" that "significantly *decreased* worker exposure *before* 1978." *Id.* 37 (emphases added). That assertion would support, not discredit, the assumption Petitioners criticize. Anyway, their evidence is suspect as it comes from a poorly documented study that interviewed ill-informed subjects. *Id.*; Resp. to Comments 44, JA____. The study also failed to provide documentation for key assumptions. Resp. to Comments 44, JA____.

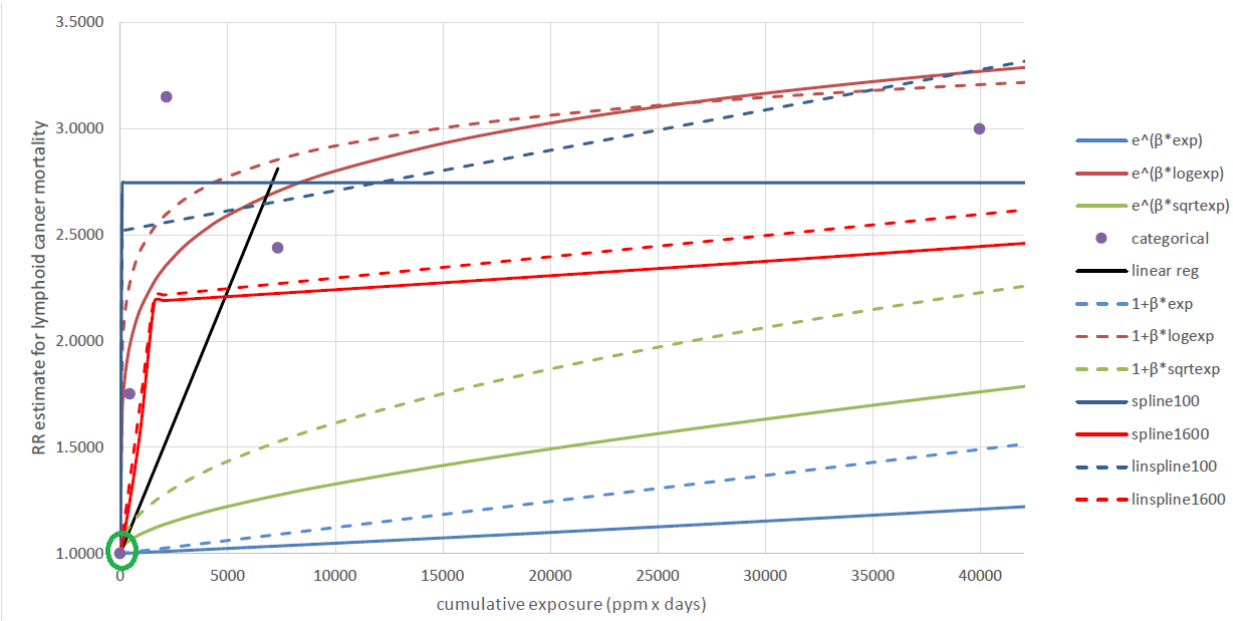
Above all, Petitioners picked the wrong fight. The exposures they latch onto here—occupational exposures in an era when ethylene oxide was not thought to be toxic—are high-level exposures. But EPA's cancer-risk estimate focused on low-level exposures. And EPA's model depicts low exposures using a different slope from what applies to high exposures. So any error in the pre-1978 exposure estimates is harmless. *See Combat Veterans for Cong. Pol. Action Comm. v. FEC*,

795 F.3d 151, 157 (D.C. Cir. 2015) (stating that in administrative law, the harmless-error rule requires the party asserting error to show prejudice). [13]

II. EPA developed its dose-response model using sound statistical methods.

At the heart of this dispute is EPA's dose-response model for lymphoid cancer. EtO Eval 4-19, JA____. The easiest, least technical way to see why EPA acted reasonably in standing by its model is to contrast it with the model Petitioners seem to prefer. Br. 49.

Consider first EPA's model, shown in Figure 4-3 of the 2016 evaluation:

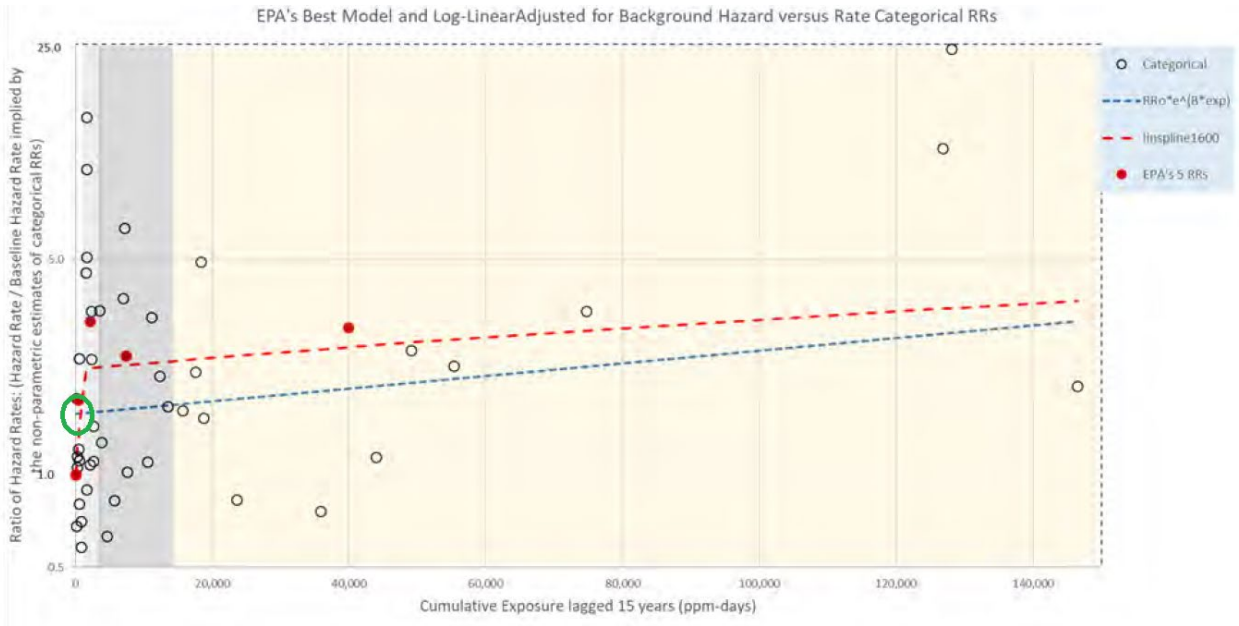


[13] In a footnote, Petitioners bemoan EPA's rejection of a study of Union Carbide Corporation's facilities. Br. 38 n.53. Arguments tucked into footnotes are forfeited. *See CTS Corp. v. EPA*, 759 F.3d 52, 64 (D.C. Cir. 2014). At any rate, EPA reasonably explained that the study's exposure assessment was "crude" for using a small number of exposure categories, only a few of which used actual measurements. EtO Eval A-28, JA____; *see id.* K-6, JA____ (calling the study "not of sufficient quality"). The study's participants also lacked women and had confounding exposures. *Id.* H-7 to 8, JA____-__.

EtO Eval 4-21, JA____. EPA's model (labeled "linspline1600") is the red hash line. Exposure is shown on the horizontal x-axis and relative cancer risk on the vertical y-axis.[14] Crucially, the y-intercept (where the red hash line crosses the y-axis and circled in green here) is 1.0: It means that when a person faces no additional exposure (x=0), she faces no additional cancer risk (y=1.0, the same as her baseline risk). Resp. to Comments 53, JA____. That comports with common sense. Indeed, all EPA's candidate models in Figure 4-3 show relative risk of 1.0 at zero exposure.

Now look at Petitioners' preferred model, in blue (while EPA's is still in red):

[14] Petitioners seize on a note accompanying Figure 4-3 (about different baseline risks in the models) and tie several arguments to it. EtO Eval 4-21, JA____; Br. 45, 47-48. But all Figure 4-3's models estimate relative risk, meaning exposed workers' cancer risk compared to unexposed workers'. That is why Figure 4-3's y-axis is labeled "RR," or relative risk. EtO Eval xi, JA____. Figure 4-3 does not address baseline risk. In other words, what Figure 4-3's note says (albeit in a somewhat awkward way)—and what the graph shows—is that the models all measure relative, not baseline, risk.



Texas Eval 150, JA____; Br. 49. Petitioners' y-intercept (also circled in green) is about 2.0. That is, Petitioners' preferred model, created by Texas, says that when a person faces no additional exposure (x=0), her risk is *twice* her baseline risk (y=2.0). Resp. to Comments 55, JA____. That makes no sense. Nor was EPA the only one to call out this flaw. One of Texas's peer reviewers did too. *Id.* 54, JA____. The absurdity of Petitioners' y-intercept justifies EPA's refusal to use their preferred model. The Court should reject Petitioners' challenge to the refusal.

Petitioners' more technical objections to EPA's dose-response model fall into three camps: (A) how EPA used the Institute's data in model development; (B) the model's fit to the data; and (C) the model's predictive powers. Br. 41-54. None of these arguments, as detailed below, has merit.

A. EPA reasonably used both individual data and categorical averages.

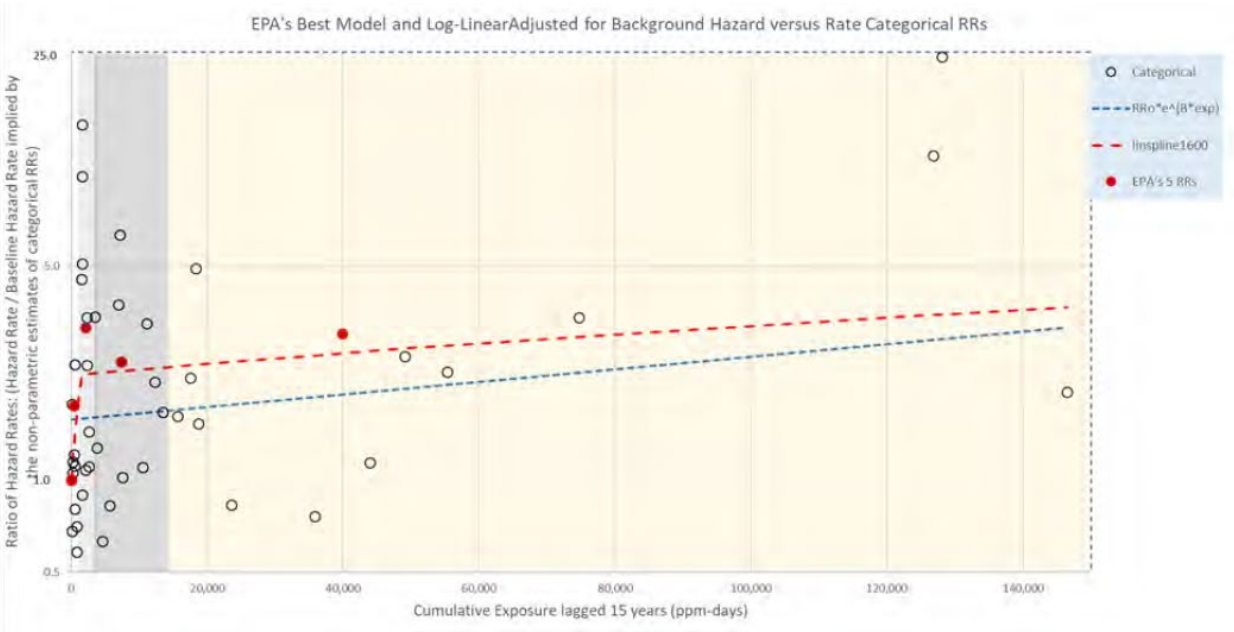
In their most complex argument, Petitioners criticize how EPA used the Institute's data to derive its dose-response model. Br. 41, 44-51. That criticism is unfounded.

To develop its model, EPA used extensive data from the Institute's study: The agency started with over 17,000 data points showing individual workers' exposure levels and cancer incidence. EtO Eval 4-3, D-65 to 66, JA____, ____-__. It then fitted 11 different models to the individual data points. *Id.* 4-19 to 21, JA____-__; *see id.* 4-15, JA____ (noting that EPA's model used "individual-level continuous exposure data"); Model Memo 1, JA____ ("[EPA] developed models fit to the original individual data in the [Institute's] cohort."); Texas Eval 142, JA____ (noting that EPA's model was "fit to the individual data").

Next, EPA compared the candidate models to see which had a better fit. In that task, "simply eyeballing" each model against the data points—over 17,000 of them—is impractical. Br. 44. There is too much noise and "unstructured information." Resp. to Comments 52, JA____. A common solution in epidemiology is to use categorical breakouts. *Id.* The idea is to turn down the noise by dividing the data points into groups and focusing on group averages.

Using this method, EPA grouped individual data points into four exposure ranges (or intervals). EtO Eval D-65 (Table D-54), JA____. Within each interval,

EPA averaged thousands of individual data points. *Id.* Each average is a categorical point.[15] *See also id.* D-5, JA____ (breast-cancer categorical breakouts). Here again are EPA's and Petitioners' preferred models. EPA's categorical points are the red dots:[16]



Texas Eval 150, JA____. Notice that EPA's categorical points reveal the shape of the dose-response relationship: At low exposure levels, more ethylene-oxide doses lead risk to skyrocket; at high levels, risk plateaus. *See* EtO Eval 4-12, JA____;

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[15] EPA had initially tried to fit its models using only categorical points. *See* Model Memo 1, JA____. But following the Science Advisory Board's advice, EPA fitted models to individual data points. *Id.*; EtO Eval 4-12, 4-15, JA____, ____. Petitioners overlook EPA's changed approach. *See* Br. 46 & n. 68 (emphasizing the board's disagreement with EPA's initial approach); *id.* 46 (confusingly claiming that EPA had "plotted estimates for each category," which "are not the individual data that EPA used in its model").

[16] There are five red dots, with four representing intervals for exposed workers and one representing the no-exposure category.

Science Advisory Board, Review of EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Aug. 2015) at 14, JA____ ("risk rises rapidly with a small amount of exposure and then rises much more gradually for even higher exposures.").

Given its focus on environmental exposure, the agency prioritized low exposures when assessing fit. *See* EtO Eval 4-15, JA____. EPA's chosen model—with two distinct slopes—reflects the epidemiological evidence that cancer risk increases faster at lower exposures than at higher exposures. *See id.* I-3, I-17, JA____, ____; Br. 44 (ignoring this evidence).

Far from "hid[ing data] from view," Br. 46, EPA reasonably organized voluminous individual data points to discern patterns within. Its chosen dose-response model thus has a "rational relationship to the characteristics of the data to which it is applied…." *Appalachian Power*, 135 F.3d at 802. Nothing more is needed to uphold EPA's statistical analysis under the "highly deferential" standard of review. *City of Portland v. EPA*, 507 F.3d 706, 714 (D.C. Cir. 2007); *see Appalachian Power*, 135 F.3d at 802 ("[W]e will not take it upon ourselves, as nonstatisticians, to perform our own statistical analysis").

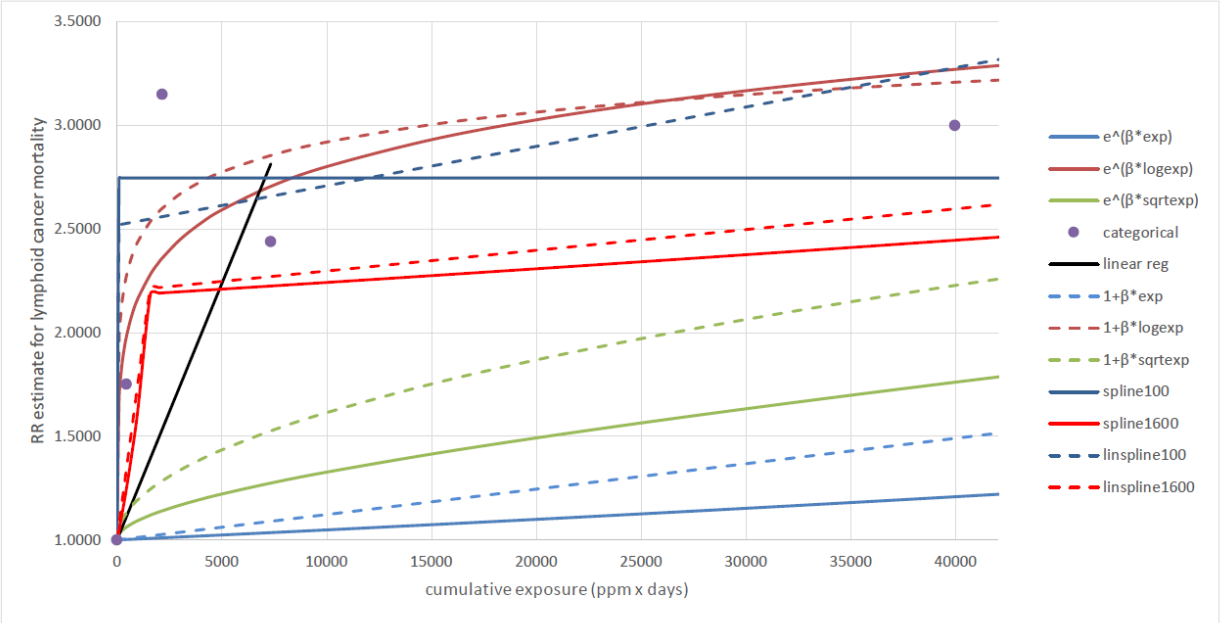
The soundness of EPA's analysis stands in sharp contrast with Texas's. Though Petitioners—pointing to Texas's white dots in the above graph—imply that Texas did not use categorical breakouts, that cannot be right. *See* Br. 49 ("The

empty circles represent the *individual* hazard rates" (emphasis added)). There are only about 50 white dots, while there are over 17,000 individual data points. So Texas must have used categorical breakouts, albeit with different—and more—intervals.

The result, a wide scatter of white dots, remains "extremely noisy." Resp. to Comments 54, JA____. All that noise hid the data's two distinct dose-response relationships. Were fit to be judged using Texas's white dots, it is anyone's guess which line, EPA's red or Texas's blue, is better, especially at low exposures. Texas's ineffective breakouts thus belie Petitioners' claim, Br. 48, that EPA used "overly-simplified" data: EPA reasonably dialed down the noise.

The final nail in the coffin for Petitioners' argument comes from Texas itself. The blue hash line shown above (and embraced by Petitioners) is an "adjust[ed]" version of Texas's model. Texas Eval 150, JA____.[17] Yet not even Texas used its adjusted model to estimate cancer risk. The actual model that Texas used (a log-linear model, also known as a Cox regression) is shown below as the bottom-most line, in solid blue:

[17] Texas said that it made this adjustment to account for the note, about baseline risk, accompanying Figure 4-3. Texas Eval 150, JA____. But the note simply explains that the models deal with relative, not baseline, risk. *See supra* n.14. It is unclear how the adjustment addresses the baseline issue that Texas perceived. Petitioners, for their part, do not even acknowledge the adjustment. *See* Br. 49.



EtO Eval 4-21, JA____ (Figure 4-3) (showing bottom-most blue line as the model e^(β*exp)); Texas Eval 154, JA____ (stating that e^(β*exp) is the functional form of Texas's model); Br. 45.

Unlike EPA's model (the red hash line), Texas's model offers only a single, gradual slope through the full range of exposures—even though the epidemiological evidence (as seen in the categorical points, in purple) shows two distinct dose-response relationships. *See* EtO Eval I-3, I-17, JA____, ____; 87 Fed. Reg. at 77,993/2 (noting Texas's model has "poor fit" at low exposures). And Texas's model predicts far lower risk than what the data shows. *See* Resp. to

Comments. 49, JA____ ("This model predicts notably lower risks than all other models under consideration.").[18]

In the end, EPA reasonably used categorical breakouts, a common method in epidemiology, to better understand the data. Its dose-response model thus reflects both the magnitude of relative risk shown in the data and the shape of the dose-response relationship. Petitioners' preferred model was not used even by its creator, Texas. And the model that Texas did use does not come close to reflecting the data. EPA thus reasonably stood by its own model.

B. EPA reasonably prioritized fit at low exposures.

Petitioners also fault EPA for supposedly miscalculating two fit metrics. As they see it, that miscalculation (over how EPA treated the model's knot) artificially improved the metrics for EPA's chosen model. Br. 42-43. Petitioners misunderstand how EPA used the two metrics.

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[18] Petitioners question models that purport to distinguish low levels of "added risk." Br. 34. Given that Texas's model predicts much lower risk than EPA's model, their criticism of EPA rings hollow.
Separately, EPA included breast cancer in its cancer-risk estimate given the strong evidence that ethylene oxide causes breast cancer. 87 Fed. Reg. 77,991/2-92/3; Resp. to Comments 23-41, JA____-__. Petitioners do not challenge that inclusion. But amicus Texas does, arguing that EPA ignored parity bias in the breast-cancer data. Texas Br. 20-22. The Court should not consider that argument. *See Michel v. Anderson*, 14 F.3d 623, 625 (D.C. Cir. 1994) ("Ordinarily, we would not entertain an amicus'[s] argument if not presented by a party"). Anyway, EPA addressed parity. Resp. to Comments 30, JA____.

To assess the fit of its candidate models, EPA considered both visual fit and two calculated fit metrics.[19] *See* EtO Eval 4-19 to 20, JA____-__. Generally, the lower these two metrics, the better the overall fit. *Id.* 4-15 & n.23, JA____. The caveat is that the two metrics speak to a model's *overall* fit across all exposure levels. But they could mask poor *local* fit.

That was so here. Though a few candidate models had slightly better fit metrics than EPA's chosen model, their visual fit at lower exposures was poor. *See id.* 4-19 to 20, JA____-__ (identifying this problem in, for example, the linear-spline model with knot at 100 ppm–days and the log-linear model with log cumulative exposure). Again, EPA focused on environmental exposure, so it reasonably prioritized local fit at low exposures above overall fit. *Id.* 4-15, JA____; Resp. to Comments 60-61, JA____-__. That was why it chose a dose-response model that has (1) good (but not the best) overall fit metrics and (2) good visual fit at low exposures. *See* EtO Eval 4-19, JA____ (noting that the chosen model has "[a]dequate statistical *and* visual fit" (emphasis added)). In doing so EPA followed the Science Advisory Board's advice to avoid rigid adherence to overall fit metrics at the expense of local fit. *Id.* I-2, JA____; Resp. to Comments 60, JA____.

[19] The two metrics are the Akaike information criterion (which measures how well the underlying data fits the model) and the *p* value (the likelihood that an observed outcome is due to chance). *See* EtO Eval 4-15 & n.23, JA____.

EPA's approach thus debunks Petitioners' argument about the fit metrics. Boiled down, the argument is that EPA made its model's fit metrics look better than they really were and "refused to re-evaluate whether that error led it to select the wrong model." Br. 43. But as explained just now, fit metrics did not dictate EPA's choice of model. Indeed, EPA rejected models with better fit metrics. EtO Eval 4-19, JA____. And EPA was crystal clear that even if it had calculated fit metrics as Petitioners urge, it would have still chosen the same model. *See* Resp. to Comments 60-61, JA____ (stating that the "key consideration" is the model's ability to "reflect the local shape (and particularly the low dose shape) of the dose response pattern."). EPA was even clearer that Petitioners' preferred calculation "would not have led to different model selection decisions in favor of the model (log-linear Cox) preferred by [Petitioners and Texas]." *Id.* 60, JA____. Texas's model, EPA said, "cannot represent any situation" where, as with ethylene oxide, "the response shape is steeper at lower as compared to high doses." *Id.* 61, JA____. Any error in EPA's calculation of the two metrics is thus harmless. *See Combat Veterans*, 795 F.3d at 157 (finding harmless error when "there is no hint of any suggestion that the [agency] would have made any different determination").

Finally, one of Texas's peer reviewers thought that even if EPA had used Petitioners' calculation, its model and Texas's would have similar fit metrics. Resp. to Comments 61, JA____. And so, the reviewer continued, "the question I

would pose to T[exas] is: why would I prefer its model over the USEPA model when the latter is clearly more health protective?" *Id.* After all, the whole point of EPA's evaluation is to assess ethylene oxide's toxicity to humans. All else being equal, EPA reasonably chose a more protective model.

Petitioners, in short, cannot undermine EPA's statistical analysis "by pointing to variables not taken into account that might conceivably have pulled the analysis's sting." *Appalachian Power*, 135 F.3d at 805. They must "identify clearly major variables the omission of which renders the analysis suspect." *Id.* Because Petitioners fail to do so, the Court should reject their arguments.

C. Texas misapplied EPA's model in its "reality check."

Petitioners' final attempt to cast doubt on EPA's dose-response model fares no better. This argument relies on Texas's "reality check" of EPA's model. Texas Eval 92-106, JA____-__; Br. 50-51. Applying that model, Texas predicted lymphoid-cancer deaths that were twice what the Institute's study had reported for sterilizer workers. Texas Eval 93-94, JA____-__; Br. 50. But the problem is not EPA's model; it is that Texas ignored the healthy-worker effect. *See also* Resp. to Comments 89-91, JA____-__ (identifying other problems in Texas's reality check).

Often seen in occupational epidemiology, the healthy-worker effect is a selection bias that leads to lower observed disease rates in a worker population

than in the general population. *Id.* 89, JA___. This effect exists because workers tend to be healthier than the average person. *Id.* 37, JA____. That is true of the sterilizer workers in the Institute's study: Their observed mortality rate from lymphohematopoietic cancers is only 72 percent that of the general population, and their rate of lymphoid tumors, 78 percent. *Id.* 90, JA____. Compared to the average person, sterilizer workers thus have lower baseline risks of lymphoid cancer.

Texas disregarded that observed difference in its reality check. It instead treated sterilizer workers as having the same baseline risk as the average person: To predict lymphoid-cancer deaths in sterilizer workers, Texas used the baseline risk for the general population. *See* Texas Eval 99, JA____ (stating that Texas calculated expected deaths using "the US population"). What Texas actually predicted, then, was lymphoid-cancer deaths in the general population, not in sterilizer workers. Resp. to Comments 89-90, JA___-__.[20]

[20] Petitioners remark, in a footnote, that EPA itself used general populations to calculate risks from certain occupational exposures. *See* Br. 51 n.77 (citing EtO Eval Tables 4-28 through 4-30, JA____-__). That argument is forfeited both for being made in a footnote and for not having been raised in rulemaking. *See CTS*, 759 F.3d at 64; 42 U.S.C. § 7607(d)(7)(B). To be clear, EPA's calculation looks at occupational exposures involved with using ethylene oxide as a sterilant or a fumigant. EtO Eval 4-99, JA____. EPA did not know the baseline risks of these users, a broader group than those who participated in the Institute's study. The agency thus used the general population's baseline as a rough estimate. And

Cont.

To see the mechanics of what went wrong when Texas ignored the healthy-worker effect, suppose that the general population's baseline lymphoid-cancer mortality is 10 out of 1,000. That is, within the U.S. population, 10 out of 1,000 people will die from lymphoid cancer. By contrast, sterilizer workers' (hypothetical) baseline mortality is only 7 out of 1,000. Meanwhile, EPA's model shows that at an exposure of 1,000 ppm–days, a person faces twice the risk of dying from lymphoid cancer compared to her baseline. *See* EtO Eval 4-21, JA____ (Figure 4-3). *What* her baseline is depends on *who* she is. An average person's baseline is 10 in 1,000. At an exposure of 1,000 ppm–days, that person's chances of dying from lymphoid cancer is 2 x (10 in 1,000) = 20 in 1,000. A sterilizer worker's baseline is 7 in 1,000, so her chances of dying at the same exposure is 2 x (7 in 1,000) = 14 in 1,000. Yet Texas calculated the *sterilizer worker's* chances by using the higher baseline for the *average person* (10 in 1,000), and compared the result (20 in 1,000) with actual sterilizer-worker deaths (expected at 14 in 1,000). Of course Texas's prediction exceeded actual sterilizer-worker deaths. The problem, in short, was user error: Texas misapplied EPA's model by using the wrong baseline mortality. There is nothing wrong with the model itself.

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anyway, the disputed cancer-risk estimate does not apply to occupational exposures. *Id.* 1-4, JA____.

Nor can a study of Norwegian workers justify ignoring the healthy-worker effect. Texas Eval 102, JA____. That study, EPA explained, defined "worker" so broadly as to cover "a very large fraction of the adult population" and make that term all but meaningless. Resp. to Comments 36, 90, JA____, ____. In addition, a study of all workers in Norway says little about the healthy-worker effect in a specific group of U.S. workers. *Id.* 36, 90, JA____, ____.

Granted, Texas's sensitivity analysis went some way toward correcting the healthy-worker bias in its reality check. Texas Eval 102, JA____; Br. 51-52. But it fell short. Though sterilizer workers' observed baseline lymphoid-cancer rates are 72 to 78 percent that of the general population, Texas treated that baseline as 84 to 85 percent. *See* Texas Eval 102, JA____ ("the T[exas] sensitivity analysis assumes [Institute] workers were 15-16% 'healthier' than the general population"). Simply put, Texas assumed that sterilizer workers were "sicker" than they were observed to be. No wonder Texas's sensitivity analysis also overpredicted worker deaths. That analysis thus does not undermine EPA's model.

To recap, in developing its dose-response model, EPA reasonably organized voluminous data to spot the relationship between exposure and risk. Then it chose a dose-response model to capture that relationship at low exposures—the exposure at issue. In all this, EPA exercised sound judgment within its area of expertise. The Court should uphold EPA's use of its model.

III. EPA's actions are procedurally sound.

All through their brief, Petitioners insist that there must be some procedural defect somewhere in EPA's action. *See* Br. 19-21, 25-30, 38-41, 54-57. Their evidence: EPA stood by its dose-response model and cancer-risk estimate in the face of their objections. *See, e.g.*, *id.* 29 (objecting to EPA's "preclusive preference" for its cancer-risk estimate), 39-40 (replaying substantive objections), 54-55 (same). Petitioners, in short, think that EPA violated procedural rules by disagreeing with them on the merits. The Court should reject their attempt to repackage their substantive arguments.

First, Petitioners say that EPA's cancer-risk estimate is not subject to "immediate judicial review." Br. 19. They are right: The estimate is not a final agency action because it "constrain[s] no one until so applied in a particular rule." *Chem. Mfrs Ass'n v. EPA*, 28 F.3d 1259, 1263 (D.C. Cir. 1994); *see Bennett v. Spear*, 520 U.S. 154, 178 (1997). But Petitioners can challenge EPA's use of that estimate in the 2020 rule. Indeed, that is why we are all here now.

Second, EPA fairly and reasonably grappled with Petitioners' many objections. Contrary to Petitioners' revisionist history, Br. 54-57, EPA responded—substantively—to those objections every time they were raised. *See supra* Argument §§ I-II (citing EPA's responses); *e.g.*, Resp. to Comments 42, JA____ (noting that Petitioners raised same comments about historical exposure

estimates in 2020 rulemaking and reproducing earlier responses), 47-52, JA____-__ (noting that Petitioners raised same comments about choice of dose-response model in 2016 evaluation or 2020 rulemaking and reproducing earlier responses), 59-60, JA____-__ (same as to knot treatment). As these examples show, Petitioners kept submitting the same comments with the same methodological flaws. *Cf.* Br. 54. And EPA reasonably continued to reject those flaws.

Third, EPA neither relied on its cancer-risk estimate "exclusively" nor gave it "preclusive" effect. Br. 27, 25; *see id.* 19-20, 25-29. For one thing, to calculate lifetime cancer risk in the Section 7412(f)(2) review, EPA used not only its cancer-risk estimate, but also estimated lifetime exposure. 84 Fed. Reg. at 69,191/1. For another, the only alternative cancer-risk estimate that commenters offered—Texas's—came from a dose-response model that is flawed. As explained earlier, EPA properly rejected Texas's estimate.[21] *See supra* Argument § II. More broadly, EPA did "consider the entire scientific record." Br. 25; *see supra* Argument §§ I-II. Then EPA rejected evidence and arguments that were scientifically and analytically unsound—as it should.

[21] Though Petitioners fault EPA for not considering Texas's unfinished estimate in the 2020 rulemaking, Br. 55-56, that argument is moot: EPA reviewed Texas's final estimate in its 2022 reconsideration. *See Daimler Trucks N. Am. LLC v. EPA*, 745 F.3d 1212, 1216 (D.C. Cir. 2013) (summarizing mootness doctrine). Anyway, EPA reasonably declined to consider an incomplete analysis.

Finally, EPA's 2016 evaluation shows consistency, transparency, and public participation. Br. 38-40. As an initial matter, the National Academy of Sciences did not review the ethylene-oxide evaluation. Rather, Petitioners spotlight procedural recommendations that the National Academy had made for EPA's evaluation of formaldehyde. Resp. to Comments 13-14 & n.11, JA____-__. So Section 7607(d)(3), which directs EPA to address National Academy recommendations, does not apply here. 42 U.S.C. § 7607(d)(3); *see* Br. 38-39.

To the extent Petitioners think that EPA's evaluation clashes with agency practice and guidance, their arguments parrot their substantive objections, and should be rejected as such. *See* Br. 39-40. Nor can Petitioners seriously think EPA's process deficient in transparency and public participation. *Id.* 39-41. At every turn, EPA invited public comment on the calculation and use of its cancer-risk estimate—in the 2016 evaluation (twice), in the 2020 rulemaking, and in the 2022 reconsideration. *See* EtO Eval App. H, K, JA____-__, ____-__; 2020 Resp. to Comments iv, JA____; Resp. to Comments, JA____-__; *see also id.* 13-14, JA____-__; EtO Eval K-1 to 2, JA____-__. And EPA explained, in great detail, why it estimated cancer risk the way it did and why it disagreed with Petitioners' objections. *See supra* Argument §§ I-II. EPA even responded to assorted objections submitted by American Chemistry Council outside comment periods. *See* Resp. to ACC Req., JA____-__; *cf.* Meeting Records, JA____-__

(documenting discussions between EPA and American Chemistry Council about the latter's comments on the 2020 rulemaking). There is no merit to Petitioners' procedural arguments. *See also* 42 U.S.C. § 7607(d)(8), (9)(D) (requiring, for alleged procedural errors, "substantial likelihood that the rule would have been significantly changed if such errors had not been made").

IV. Petitioners forfeited their nondelegation argument, which, in any event, lacks merit.

Petitioners aim their final salvo at Congress, contending that it impermissibly delegated legislative authority in Section 7412(f). Br. 57-59. That argument is both forfeited and meritless.

The Court cannot consider the nondelegation argument because—as Petitioners concede, Br. 59 n.88—they failed to raise it in the rulemaking. The Clean Air Act's mandatory exhaustion rule allows judicial review only of objections raised with reasonable specificity during the public comment period. 42 U.S.C. § 7607(d)(7)(B). This Court "strictly enforce[s]" the requirement—including against belated nondelegation arguments. *Growth Energy v. EPA*, 5 F.4th 1, 24 (D.C. Cir. 2021) (per curiam); *see Heating, Air Conditioning & Refrigeration Distribs. Int'l v. EPA*, 71 F.4th 59, 65 (D.C. Cir. 2023), en banc *rehearing denied*, 2023 WL 5416965 (Aug. 18, 2023) (refusing to consider nondelegation argument not raised in rulemaking). It should do so again here.

Trying to excuse their failure to exhaust, Petitioners say that their argument "depends on a change in Supreme Court precedent" as stated in the dissent from *Gundy v. United States*. Br. 59 n.88; 139 S. Ct. 2116 (2019). That argument, Petitioners continue, "could not have been brought before the agency." Br. 59 n.88.

They are wrong both factually and legally. As a factual matter, *Gundy* was decided in June 2019—six months *before* EPA proposed using the cancer-risk estimate, for the first time, in the 2020 rulemaking. 84 Fed. Reg. at 69,182. Petitioners could have raised their nondelegation argument when commenting on the proposal or later in the 2022 reconsideration. As a legal matter, *Gundy* did not "change" nondelegation law. Br. 59 n.88. Even Petitioners admit that their preferred test—from the dissent—is "not binding." *Id.* 59.

More to the point, there is no acceptable excuse for failing to raise the nondelegation argument to EPA: When a statute requires exhaustion, courts "cannot excuse a party's failure to exhaust, no matter the reason." *Fleming v. USDA*, 987 F.3d 1093, 1098 (D.C. Cir. 2021). The Court should not consider the nondelegation argument.

Even if the Court were to reach the merits, it should uphold Congress's delegation. The Supreme Court has, "time and again," said that a statutory delegation is allowed so long as Congress lays down an "intelligible principle" to

guide an agency's exercise of authority. *Gundy*, 139 S. Ct. at 2123 (plurality op.). That standard is "not demanding." *Id.* at 2129. All kinds of broad delegations have passed muster, including delegations to regulate in the "public interest" and to issue air-quality standards that are "requisite to protect the public health." *Id.* (collecting cases).

Section 7412(f)(2) easily clears the bar. In it, Congress spelled out exactly how much risk triggers EPA's duty to set more standards, and how protective they must be: If a standard regulating a carcinogenic pollutant does not "reduce lifetime excess cancer risk to the individual most exposed to emissions from [a regulated source] to less than one in one million," EPA "shall" promulgate standards. 42 U.S.C. § 7412(f)(2).[22] Those standards, moreover, must provide an "ample margin of safety to protect public health." *Id.* (directing EPA to also consider cost and other factors). Far from abdicating its legislative authority, Congress exercised that authority in Section 7412(f)(2) while setting intelligible principles to guide EPA. Br. 57-59. There was no impermissible delegation.

[22] *See also* 42 U.S.C. § 7412(f)(2)(B) ("nothing in subparagraph (A)…shall be construed as affecting, or applying to the Administrator's interpretation of this section, as…set forth in the Federal Register of September 14, 1989 (54 Federal Register 38044)."); 54 Fed. Reg. at 38,044/3-45/3 (explaining that EPA generally presumes risk of no higher than 1 in 10,000 to be acceptable, and then considers other health and risk factors to complete an overall judgment on acceptability).

CONCLUSION

EPA tightened standards for certain ethylene-oxide emissions because those emissions posed unacceptable risk to public health. In making that determination EPA used its cancer-risk estimate for ethylene oxide. It calculated cancer risk using high-quality data and applied sound statistical analysis. The Court needs nothing more to "ascertain[] the lay of the land" and uphold EPA's actions. *Appalachian Power*, 135 F.3d at 802. It should deny the petitions for review.

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CERTIFICATES OF COMPLIANCE AND SERVICE

I certify that this brief complies with Fed. R. App. P. 32(a)(5) and (6) because it uses 14-point Times New Roman, a proportionally spaced font.

I also certify that this brief complies with Fed. R. App. P. 32(a)(7)(B) because according to Microsoft Word's count, it has 10,352 words, excluding the parts of the brief exempted under Rule 32(f).

Finally, I certify that on October 30, 2023, I electronically filed this brief with the Court's CM/ECF system, which will serve each party.

/s/ Sue Chen
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