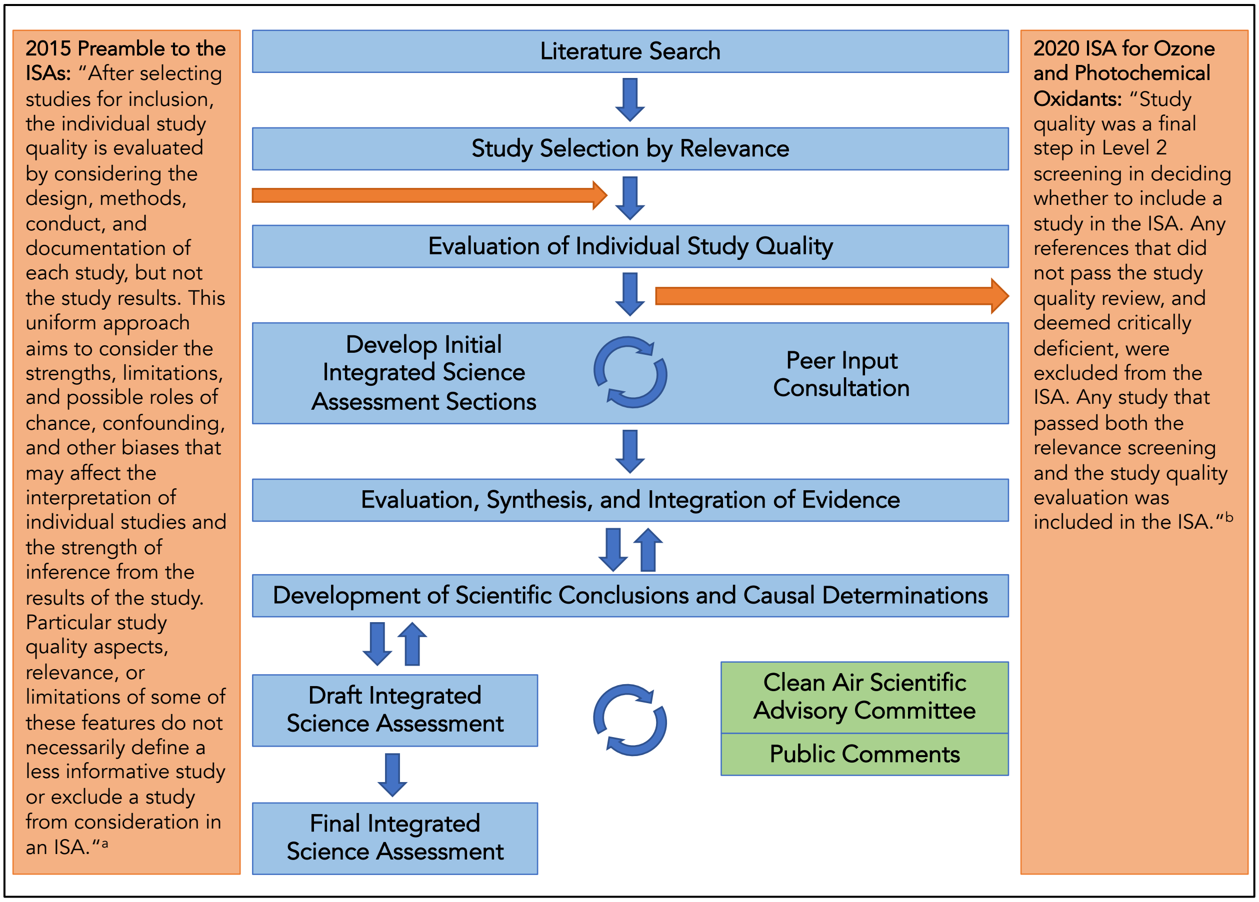
Supplementary Digital Content



eFigure 1. Schematic of the Integrated Science Assessment development process. The boxes in blue indicate the EPA's process (top to bottom). The boxes in green depict input from the Clean Air Scientific Advisory Committee and the general public. The boxes in orange describe the EPA's approach to study quality in 2015 (left) and 2020 (right). The 2015 approach has an inward-pointing orange arrow, indicating study quality considerations that go into the evaluation of literature. The 2020 approach has an outward-pointing orange arrow, indicating the exclusion of literature deemed "critically deficient". Adapted from the 2015 Preamble to the Integrated Science Assessments[a] and the 2020 ISA for Ozone and Photochemical Oxidants[b].

eTable 1. Study quality criteria outlined by Goodman et al.[c] for weight-of-evidence analysis of short-term ozone exposure and asthma severity. Comments refer to context provided by studies in the epidemiology literature.

Criterion	**Study Design**	**+1**	**-1**	**Comments**
Study design		Panel studies Case-crossover studies	Time-series studies	Panel studies and case-crossover studies are also subject to biases, and magnitude and direction of bias depend on how specifically a study is implemented.[d,e]
Study size	Panel studies	>= 50 cases and/or >= 500 measurements	< 50 cases and/or < 500 measurements	Presumably, criteria related to sample size are intended to ensure that results are statistically significant. However, the epidemiology community widely accepts that statistical significance is often overinterpreted as proving or disproving a hypothesis, when assumptions built into statistical tests invalidate such judgments.[f]
	Case-crossover studies	>= 100 cases	< 100 cases	
	Time-series studies	>= 1 year	< 1 year	
			Not reported	
Selection bias	Panel studies	>= 70% compliance in health outcome measurements or authors addressed missing data (e.g., by determining if pattern in missing data was random)	<70% compliance in health outcome and authors did not address missing data	Reliance on strict selection criteria does not make sense when there are many varieties of selection bias that can have different effects on the study outcomes.[g] Bias depends on the structure of the data, not whether or not the data were missing at random.
	Case-crossover studies	Time-stratification or bidirectional method	Unidirectional method	

	Time-series studies	N/A	N/A	
Exposure assessment	Panel studies	Monitor < 10 km	Monitor > 10 km	These criteria assume that distance from a monitor is the only factor that affects exposure measurement errors, and it assumes a cutoff value which might not be appropriate for all air pollutants, since spatial variability differs among air pollutants as a function of their atmospheric chemistry and sources.[h]
	Case-crossover studies	Grid cell < 10 km or Monitor < 10 km	Grid cell > 10 km or Monitor > 10 km	
	Time-series studies	Average of multiple monitors Monitor < 10 km	Monitor > 10 km	
			Insufficient information provided	
Outcome assessment	Panel studies	Symptoms or spirometry measurements by medical professionals	Symptoms reported by subjects or caretakers Lung function tests without clinical supervision	Discrepancies between discharge diagnoses and hospital databases indicates bias due to diagnostic error among medical personnel. Strict criteria do not prevent bias in outcome assessment.[i]
	Case-crossover studies	ICD codes clearly specified	ICD codes not clearly specified	
	Time-series studies	ICD codes clearly specified	ICD codes not clearly specified	
Statistical approach	Panel studies	Generalized estimating equations Linear mixed models Generalized linear models	Other models	Model choice depends on the input dataset and the research question. If the model design allows for addressing certain types of bias, such as day of the week, it might be appropriate. Within those constraints, different options may be
	Case-crossover studies	Conditional logistic regression	Other models	

	Time-series studies	Generalized estimating equations Poisson regression	Other models	appropriate.[j,k,l] For example, at times generalized additive models may be used in time-series studies.[l] Not all conditional logistic regression models are valid for case-crossover studies.[c]
Confounding		Considered at least one factor for each category: Temporal trends Temperature Relative humidity or dew point temperature “Other” (day of week, time spent outdoors, holidays, school schedules, occurrence of flu or other respiratory disease)	Study did not consider at least one confounder from each category	Potential confounders to be tested in the model should depend on the specific research questions[m] rather than following a prescribed list.
Adjustment for pollen		Included pollen	Did not include pollen	There is low correlation of tree and weed pollen with $PM_{2.5}$ and O_3, suggesting that pollen is not likely a confounder of the relationship between either $PM_{2.5}$ or O_3 with health effects.[n]
Multiple lag times		Evaluated multiple lag times	Did not evaluate multiple lag times	Omission of lags may be a source of bias, but the choice and inclusion of lags also depends on the research question. For example, proper selection of lags is important for studies of

				birth outcomes and child health.[o] In some cases, lags can introduce bias.[p]
Sensitivity analyses		One or more sensitivity analyses	No sensitivity analysis	Sensitivity analyses can provide useful tests for uncontrolled confounding but are often based on assumptions that cannot be tested.[q]

eReferences

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