

Preliminary Comments on the ISA from Dr. Aaron Cohen

Comments on Chapter 5: Integrated Health Effects of Exposure to Sulfur Oxides

General Comments

The authors have done an impressive job, summarizing in a generally clear and efficient manner a large and complex literature and its evolution since the previous ISA. The links to Chapter 3 (exposure) and Chapter 4 (dosimetry) are very helpful and serve well to buttress arguments made concerning the health evidence.

The authors have largely addressed concerns that I expressed in my comments on the previous draft and I now concur with the causal determinations they have made with regard to the eight classes of health outcomes.

Section 5.2.1 Respiratory effects - Short-term Exposure

This section effectively presents the evidence for a causal effect based on the evidence for the exacerbation of asthma from both observational and experimental studies. The key role of experimental studies, which provides clear evidence of an effect of SO₂ per se, is well described, and the crosswalk between the animal and human evidence with regard to lags and levels of exposure, the dosimetry and mode of action (Chapter 4) is compelling.

Page 5-6, line 29: why “In contrast...”?

Page 5-35, line 4: Why are the controlled human exposure studies not interpretable as effects of SO₂ per se?

Page 5-47, line 9-12: This seems a bit of a reach.

Page 5-35, line 16: I could find no previous discussion of “potential differential exposure error.”

Page 5-39, line 1-5: Significance of stratum-specific estimates is not the issue: was there evidence of a trend in effects?

Page 5-39, line 23: Why “In contrast?” Tunnicliffe et al. (2003) seems to corroborate Linn et al. (1983b).

Pages 5-65-5- 66/ Page 5-71, lines 33-36: **Concentration-response relationship** Although I think the authors have presented the available studies well, I still find the treatment of this issue is overly confident with regard to linearity given the very limited empirical exploration of this

1 issue. More definitive results will likely require much larger studies and more comprehensive
2 and flexible exploration alternatives to linearity

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4 Section 5.2.2 Respiratory effects - Long-term Exposure

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6 The determination that the evidence is now “suggestive” of a causal relationship rather than
7 “inadequate,” rests on two new studies of asthma incidence in children and several experiments
8 in rodents. In The experimental studies are key because they serve to mitigate to some extent
9 considerable concerns with attributing the observed effects to SO₂ per se, as opposed, for
10 example, to sulfate particles, given that neither epidemiologic study provided information on co-
11 exposures. As the authors note, Chapter 4 also provides some mechanistic support for this
12 determination.

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14 The authors have, to some extent addressed issues raised in the review of the previous draft
15 regarding confounder control in the two longitudinal studies of asthma incidence, but an explicit
16 discussion of which risk factors in addition to air pollution are most important to assess re.
17 confounding and effect measure modification, and what surrogates for them are effective, would
18 still be helpful.

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20 Section 5.3.1 Cardiovascular effects - Short-Term Exposure

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22 The revised section provides a more critical and balanced assessment of the available evidence,
23 including more critical assessment of the potential for confounding by co-pollutants, and I
24 concur with its determination that despite the accrual of many new studies since the last ISA, the
25 strength of the evidence remains “inadequate.” The contrast with the evidence re. short-term
26 exposure on respiratory effects, especially the relative lack of support from experimental studies
27 is telling.

28
29 Chinese studies have tended to observe effects on cardiovascular outcomes of short-term
30 exposure to SO₂, e.g., on hospital admissions and ED visits (Page 5-194, lines 7-13) and
31 mortality (Page 5-198, lines 4-11). Given the dominant role of coal burning in air pollution
32 exposure and disease burden in China, it would be critical to control for the most relevant
33 pollutants, i.e., PM_{2.5} or, better yet, sulfate PM, which has been done in few if any Chinese
34 studies.

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36 Section 5.3.2 Cardiovascular effects - Long-term Exposure

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38 The determination that the evidence regarding cardiovascular effects of long-term exposure to
39 SO₂ is “inadequate” to make causal determination is well-supported by the evidence reviewed in
40 this section.

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1 Page 5-291, lines 9-12 and Table 5-32: The SO₂ estimate for MI incidence from Lipsett et al.,
2 1.98 (0.07-60), is so imprecise that it contributes virtually no information.

3
4 Table 5-33 and Page 5-22, lines 24-31: same comment as above with respect to stroke.

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6 Page 5-221, lines 6-9: Without consideration of PM_{2.5} or sulfate PM these Chinese estimates
7 cannot be interpreted as effects of SO₂.

8
9 Section 5.3.2.4: Are these longitudinal or cross-sectional studies? Presumably the latter, but if
10 not, more information is needed on cohort follow-up (numbers of repeat measurements, over
11 how many years, loss to follow-up, etc.)

12
13 General comment on the Tables (5-32 to 5-34): Please provide the number of events (e.g., MI,
14 stroke, hypertension, etc.) in addition to cohort size.

15 16 Section 5.4 Reproductive and Developmental Effects

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18 The determination that the evidence effects is “inadequate” to make causal determination is well-
19 supported by the evidence reviewed in this section. There is no reason to attribute the observed
20 effects of exposure to SO₂ per se given that the role of co-pollutants has generally not been
21 addressed in the epidemiologic studies (which also report effects of PM, CO and NO₂ on adverse
22 reproductive outcomes), and the lack of experimental evidence which would support such an
23 association.

24 25 Section 5.5.1 Total mortality - Short-term exposure

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27 The revised chapter provides stronger support for the determination that the evidence remains
28 “suggestive” of a causal relationship and documents more clearly that despite the accrual of more
29 studies, the shortcomings of the literature identified in the 2008 ISA have largely not been
30 addressed. Specifically, the potential for confounding of observed SO₂ effects by co-pollutants
31 remains largely unresolved and, to the extent that confounding by co-pollutants has been
32 assessed, neither PM_{2.5} nor sulfate PM has been included, a particular issue in Chinese studies
33 where coal burning is A, if not *the*, major source of pollution.

34
35 The authors correctly note that the exploration of exposure-response relationships has been
36 “limited,” but still argue that a log-linear model best describes the relationship between short-
37 term exposure and mortality (Page 5-274, lines 12-21). However, neither Figure 5-24 nor Figure
38 5-25 appear to support this view.

1 Section 5.5 Total mortality - Long-term exposure
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3 Despite the accrual of new studies that observe effects of long-term exposure on mortality, the
4 determination that the evidence regarding mortality and long-term exposure to SO₂ is
5 “inadequate” to make causal determination is generally well-supported by the evidence reviewed
6 in this section.
7

8 Page 292, lines 27-30: This seems to be the “bottom line.” I would consider leading with it.
9

10 Table 5-42: Please give the number of deaths (all-cause and cause-specific) and total size of the
11 cohort at entry.
12

13 Page 5-291, lines 24-31: These are issues with regard to generalizability as opposed to internal
14 validity and probably do not belong here.
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16 Section 5.5 Cancer - Long-term exposure
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18 The determination that the evidence regarding cancer and long-term exposure to SO₂ is
19 “inadequate” to make causal determination is well-supported by the evidence reviewed in this
20 section, including the conclusions of other authoritative sources and expert groups.
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22 The authors should note specifically that two of the three largest studies accrued since the last
23 ISA (Krewski et al. 2009 and Brunekreef et al. 2009) report null results for lung cancer. A
24 summary table and/or forest plot would be helpful in presenting the epidemiologic studies.
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