

APPENDIX A

HEALTH EFFECTS

Appendix A - Ozone Health Effects: Executive Summary

The Clean Air Act states that the primary National Ambient Air Quality Standard shall be "requisite to protect public health...allowing for an adequate margin of safety". In proposing a change from the current 0.12 ppm daily maximum 1-hour average value not expected to be exceeded more than once per year on average over a three year period to a daily maximum 8-hour average standard that is attained when a 3-year average of third highest annual values does not exceed 0.08 ppm, EPA relies primarily on three types of health effects information, as cited in its Criteria Document (CD), Staff Paper (SP) and Federal Register notice (FR). These data include 1) chamber studies where volunteers are exposed to constant ozone levels under vigorous exercise for 6.6 hours, with short breaks for medical evaluations and lunch; 2) camp studies that measure responses of children performing daily activities at summer camps whose exposures are estimated from ambient ozone monitors located nearby; and 3) hospital admissions studies where NYC hospital admissions are compared to ozone levels in the metropolitan area. The biological responses and ozone exposures observed in these studies were used to construct dose-response functions. The dose-response data were combined with modeled distributions of population ozone exposure to predict either the percentage of people experiencing at least one particular response per year or the number of times a particular response occurred within the exposed population.

In comments below, API makes a compelling case that the EPA risk assessment, used by the Agency to justify a more stringent standard, is fundamentally flawed. Our detailed comments address a number of reasons why this is so, including:

- Failure of the modified risk assessment to refute the CASAC findings of no significant differences in health protection among alternative standards;
- Failure to recognize the increased margins of safety afforded by current standards, resulting from conservative EPA monitoring and modeling policies;
- Over-reliance on the results from the EPA exposure chamber facility- a chamber likely contaminated with several artifact pollutants;
- Use of unrealistic dosing regimens in EPA exposure chamber;
- Ascribing summer camp study response and asthmatic admissions wholly to ozone exposures;
- Failure to consider new evidence that ozone risks are over-estimated.

API's evaluation of EPA's interpretation of the underlying health studies and the agency's use of ozone exposure and risk models indicate that risks predicted by the Agency may be overestimated by over an order-of-magnitude for the most susceptible group identified by the Agency, outdoor children. Risk assessments for the next most sensitive EPA group, outdoor workers, are lower by factors of 2 to 10 below those calculated for outdoor children. Health risks of the general population who are indoors more and exercise less are lower still. By use of overly conservative risk assessment approaches, EPA has made public policy decisions that are not supported by the science. API offers evidence that residual risk levels evaluated quantitatively by the Agency and judged acceptable for the proposed standard are already being provided by existing regulations.

1) EPA's modified risk assessment does not negate CASAC's finding of no significant difference in health protection among the current and alternative standards.

CASAC, impaneled to evaluate the technical bases of revision of the ozone standard, found that in EPA's estimate of risks to outdoor children, none of the alternative standards under consideration were significantly more protective. Indeed, CASAC found "that there is no 'bright line' which distinguishes any of the proposed standards (either the level or the number of allowable exceedances) as being *significantly* more protective of public health," Specifically, as CASAC concluded in its closure letter: "... the differences in the percent of outdoor children [cite] responding between the present standard and the most stringent proposal (0.07 ppm/8HR/1EX) are small and their ranges overlap for all health endpoints."

Similarly, reviewing EPA's risk assessment of estimated ozone-related hospital admissions in New York City, CASAC found that there were only small differences between the number of admissions estimated for ambient concentrations at the level of the current standard and those estimated for any of the alternative standards. Accordingly, the Agency notes that CASAC recognized [61 FR 65727] that "the selection of a specific standard level [within the range of evaluated alternative standard risks] is a policy judgment."

In response to these CASAC findings, the Agency modified the 1995 version of the risk table originally reviewed by CASAC to include both central tendency point (median) estimates of risk and ranges that, in EPA's view, allowed the Agency to distinguish among alternative standards [61 FR 65725]¹. In discussing CASAC's conclusion that there would be no significant increase in public health protection resulting from the standard changes under consideration, the Agency gives three arguments to explain its disagreement: 1) that the small differences in median percent response are *statistically* significant within cities; 2) that CASAC failed to appreciate that these small percentage changes represented "hundreds of thousands of times that children would likely experience such effects,"; and 3) that CASAC was confused by differences among cities that obscured differences among standards [61 FR 65728].

EPA's first argument appears to miss CASAC's point that the differences in protection afforded by alternative standards were considered small and not medically or clinically significant enough to warrant distinguishing among them. As noted in the proposal, "...some CASAC members and others have suggested that it is difficult to determine if a margin of safety exists for any particular level and therefore, in their opinion, the differences in health protection may not be significant enough to justify a change from the current standard" [61 FR 65729]. Furthermore, EPA's statistical

¹ EPA's FR notice did not modified revised risk estimates for its newly-proposed standard. The Agency believes that risks associated with the proposed standard lie between those projected for the 0.08 ppm standards with one and five expected exceedances. Similarly, a proposed 0.09 ppm 8-hour standard with three exceedances is thought to provide a level of protection comparable to that projected for the current 0.12 ppm hourly standard [61 FR 65731/32]. On February 20, 1997 EPA announced a "supplemental" ozone health risk assessment evaluating the proposed standard. Due to severe time constraints, API has only performed a limited evaluation of EPA's new risk assessment but intends to submit more detailed comments for EPA consideration at a later date.

significance argument is fallacious because small differences that truly exist between *modeled* risks can be made to be statistically significant simply by increasing the number of model runs used to generate median estimates.

EPA's second argument in response to CASAC's conclusion incorporates a redefinition of the health endpoint that makes the same effect look larger and of potentially more concern. *This is accomplished by changing the units of measure from the number of people affected to the number of times the effect is likely to occur within the entire population.* However, because of the importance EPA places on repeated exposures, the number of occurrences per individual is the more relevant measure of health protection. The EPA risk analysis [Whitfield et al., 1996] used to generate the proposal risk table, assumes a constantly sensitive sub-population of individuals who always respond reproducibly to the effects of ozone exposure. However, attenuated responses to repeated exposure, temporal hormonal influences on breath NO and ozone sensitivity, and lack of individual subject dose-response in EPA 6.6-hour chamber studies demonstrate this key assumption to be false.

The impact of EPA's falsely assuming a small, constant "responder" population vs. widely distributing health effects over the entire population can be illustrated with Whitfield's risk simulations for the Washington, D.C. area. If one assumes, as does Whitfield, that the same children always respond to ozone, 7.5 to 8.0 annual responses (FEV² decrement \geq 15%) per child are estimated for the 0.09 ppm/8HR/5EX and 0.07 ppm/8HR/1EX at proposed standards, respectively. However, if the total number of annual responses estimated were distributed across the total D.C. population of outdoor children (a more likely scenario), the number of annual responses per child then drops to 0.29 - 1.0, well within the non-adverse "nuisance" effect frequency identified by CASAC [61 FR 65723]. In this case the "hundreds of thousands of times that children would likely experience such effects" is reduced to one or less occurrences per child per year.

EPA's third rebuttal of CASAC conclusions attributes the overlap in health protection afforded by alternative standards noted by CASAC to climatic and demographic differences among cities rather than to differences among standards. This explanation is puzzling, inasmuch as 1) considerable effort was expended by EPA in adjusting air quality distributions city-to-city to simulate comparable marginal attainment for each city, 2) a common activity database was used for each city, and 3) the primary impacts of meteorological variables are on air quality which is normalized to attainment status among cities.

2) Recent research results and analyses indicate that actual personal ozone exposure is less than that estimated by EPA and greater protection is afforded by current standards.

The ozone probabilistic NAAQS Exposure Model (pNEM/ozone) is an integral part of the EPA risk assessment that forms the basis of the proposed standard. Although under active development and use over the past decade, pNEM/ozone has never been validated. API recently conducted a 1995 pilot study of ozone concentrations in the Los Angeles basin using personal ozone monitors

² FEV = forced expiratory volume in one second .

[Johnson et al., 1996]. A comparison of personally monitored ozone concentrations to those predicted from ambient monitors by pNEM/ozone indicated that the current model values exceed the personally monitored values. Monitored values averaged only 50 - 60% of modeled personal concentrations.

The pNEM/ozone model simulations used in the ozone risk assessment overestimate actual personal exposure. A number of possible reasons for such overestimates are outlined below.

- Unrealistic Estimates of "Motivated Exercisers". The current pNEM model incorporates an insupportable assumption treating the entire population as "motivated exercisers". This is an important issue, since the effects of ozone on people are influenced not only by ozone concentrations, but also by how much air people breath. Higher ventilation rates result in greater effects at a given ozone level. Because of the relatively high breathing rates (about 60 liters/minute for adults, compared to normal rates of 10 - 15 liters/minute) required to experience effects at 1-hour exposures to 0.12 ppm ozone, the assumption that 100% of the population are "motivated exercisers" (i.e. physically able and willing to sustain such prolonged, elevated breathing rates) is particularly extreme. Few, if any, normal exercisers will maintain such breathing rates continuously for an hour. As a result, only a fraction of the risk projected for the current standard is likely to occur. Less than half of the population is physically fit or willing enough to maintain these breathing rates with any frequency, even if "motivated" [USHHS, 1996].
- Failure to Account for Fixed-site Ambient Monitor Interferences and Inlet Heights. As discussed in the ozone Criteria Document (CD), the current network monitors (both UV and chemiluminescence types) are subject to a number of interferences that, in general, cause the monitors to report inaccurately high ozone values, particularly during episodes of high ozone [CD, 3-90ff]. In addition, current EPA ambient monitor siting guidance may also contribute to overestimates of personal ozone exposure by requiring inlets to be installed 3 to 15 meters above grade. Recent studies of vertical ozone gradients indicate that ozone concentrations frequently increase with height above the ground, with measured increases in ozone levels from 2 to 10 meters averaging 13% [Wisbith et al., 1996]. The current pNEM/ozone model does not correct for these effects and so may over predict ozone exposure accordingly.
- Mischaracterization of "Outdoor Children" Activities

Johnson et al., 1996b use three criteria to define "outdoor children" and compile a characteristic activity database for exposure modeling: a least one winter weekday diary day with more than 2 hours outdoors, or at least one winter weekend day with more than 3 hours outdoors, or at least one summer (June-August) day with more than 4.5 hours outdoors. Since most of the subjects in the child activity database report only a single diary day, eliminating the "non-criteria" subject days in constructing the annual sequences of daily activities for "outdoor children" grossly distorts their modeled behaviors. In such single day data sets, this approach ensures that every child spends 2 hours outdoors on every winter weekday, 3 hour outdoors on every winter weekend day, and 4.5 hours outdoors on every

summer day. In ascribing such activity patterns to 40% of the child population, the pNEM/ozone modeling effort for this cohort should greatly overestimate likely ozone exposures.

- **Failure to Correct for other Exposure Modeling Uncertainties and Assumptions.** The current version of pNEM/ozone fails to account for a number of other effects that may reduce personal exposures compared to the values reported by fixed-site monitors. For example, reductions of ozone in near-roadway and in-vehicle microenvironments from the reaction of ozone with nitric oxide (NO) emitted by automotive exhaust are ignored in the current EPA exposure model. In coordination with OAQPS staff, API has modified the pNEM/ozone model to account for a number of missing variables and explored the quantitative impact of other, more subtle, assumptions [Johnson, 1996]. The net effect of these modifications is a more realistic version of the pNEM/ozone model that projects substantially less population exposure than the EPA version used in the proposal. For outdoor workers (who, for comparison's sake) were assumed to be motivated exercisers, modeled exposure reductions averaged 20-30% for 1-hour exposures and about 60% for 8-hour exposures. Although not specifically modeled, comparable reductions would be expected for the outdoor children. The combined effects of model improvements and questionable assumptions indicate that exposures predicted by the current version of pNEM/ozone may be overestimated several-fold. Consequently, risks tabulated in the proposal are overestimated and levels of protection afforded by existing standards may substantially exceed those assumed by the Agency.

3) EPA relies inappropriately on chamber results that produce the greatest effect.

Agency projections of FEV decrement risks were derived exclusively from EPA chamber studies. The results of other comparable studies, while recognized and even analyzed by EPA, played no role in the final risk assessment estimates. Sole reliance on one set of data to the exclusion of others appears an imprudent policy and contrary to the Agency's stated "weight-of-the-evidence" approach for assessing the relevance of scientific data. The responses reported by EPA researchers are substantially higher with lower effect thresholds than those reported from other investigators, using different chambers, but with similar protocols. For example, the 6.6-hour EPA studies report group mean FEV decrements of about 13% at 0.12 ppm and 7-8% at 0.08 ppm of ozone. In contrast, Horvath and his colleagues, report only a 2% group mean decrements at 0.08 ppm and Linn et al report decrements of 2-4% at 0.12 ppm for 30 L/minute breathing rates.

Although the Agency points to modest protocol differences as leading to these markedly lower responses, another reason that EPA responses may be higher is the possibility that other respiratory irritants were present in the EPA chambers. Agency chamber studies use a process, that in addition to forming ozone, also forms organic respiratory irritants, such as aldehydes and peroxides, and other new species not encountered in ambient air. In addition, steam injected to maintain humidity control in the EPA chamber was contaminated with a volatile tertiary amine, a substance used to control steam pipe corrosion, that has reported respiratory irritant properties. API's concerns with EPA chamber artifacts potentially biasing the responses of volunteers has been repeatedly presented

to CASAC over the past decade. In response, CASAC members have asked that a discussion of this issue be included in the Criteria Document; however, the Agency has refused and dismisses this concern as a "red herring" [USEPA, 1995a,c].

4) Ozone Chamber Studies Relied Upon by EPA Use Unrealistic Exposure Regimens

Exposure chamber research plays a predominate role in risk assessments conducted for the current rulemaking. The estimated degree of reduced forced expiratory volume in one second (FEV), measured as a function of ozone exposure, is used in the EPA risk assessment to project risks for various populations³. The chamber studies that form the core of the EPA risk assessment use artificial dosing profiles that have little counterpart in the real world. In these studies subjects are exposed to constant ozone concentrations for 6.6 hours at constant breathing rates of 40 liters per minute for 50 minutes of each hour with at-rest breathing for the remaining 10 minutes. The 6.6-hour exposure patterns are unrealistic on three counts:

- First, to the extent the EPA 6.6-hour studies were meant to simulate a day of "heavy to severe manual labor" by outdoor workers, the group mean exercise level chosen (40 L/min) appears to exceed the 30 L/min group mean breathing rate reported by Linn et al., (1993) for outdoor construction workers doing the most strenuous jobs. Although the 40 L/min rates may be realistic for the hardest-working individuals (only 3 or 4 of the 19 Linn et al. workers were close to the 40 L/min rate), they clearly overestimate breathing rates of typical construction workers. Population risks estimated for such prolonged exercise patterns need to be reduced several-fold to account for the modest fraction of individuals even within such high-exercise groups who will maintain such strenuous, multi-hour working patterns.
- Second, constant ozone levels used experimentally do not simulate ambient ozone levels that vary diurnally, typically peaking in the early afternoon with lower concentrations during the mornings and evenings. A study by Hazucha et al., (1992) exposed subjects to an 8-hour triangular ozone concentration pattern ranging from 0 ppm to 0.24 ppm at mid-exposure to 0 ppm and averaging 0.12 ppm over the 8-hour exposure period. Although the group mean FEV decrement (10.2%) peaked at 6 hours, group response had recovered to only a 6% decrement after 8 hours, about the same value (5%) reported for this group after 8 hours at a constant 0.12 ppm exposure. These important results clearly suggest that dose-rate (or ozone concentration) is more important than total dose and that respiratory decrements quickly adapt to changing exposures.
- Finally, the constant breathing rates used in the 6.6-hour studies are not typical of sensitive populations identified by EPA, in that they fail to mimic natural breathing rate variations during exercise. Recent studies monitoring breathing rates in children, outdoor workers, and outdoor construction workers [Spier, et al., 1991; Shamoo et al., 1991; Linn et al., 1993]

³ Curiously, EPA fails to point out that repeated exposure to ozone over several consecutive days results in progressively *less* response as measured by FEV changes.

indicate highly variable patterns. The apparent dose-rate effect reported by Hazucha et al., 1992 and Adams et al., 1997 suggests that breathing rate variability is an important parameter controlling functional decrements.

5) EPA's interpretation of the summer camp studies is flawed because such studies do not evaluate exposures solely to ozone and cannot serve as a basis for ascribing observed adult responses to children. EPA over-interprets risks from ozone exposure, based on hospital admissions data.

Use of summer camp studies relating lung function decrements to ozone exposure is limited because researchers generally do not account for responses caused by exposures to other irritant species, such as allergens (pollen, mold spores, dust) or differing exercise levels among children. Kinney et al. [1996] reanalyze six summer camp studies and report a seven-fold range of ozone sensitivity across studies, suggesting confounding by other pollutants or mechanisms. A mean FEV decrement of 2.7% is found across studies for 0.12 ppm ozone exposures; however, this mean response is halved when corrected for the effects of children becoming more proficient in conducting the respirometer tests during the period of the studies, a fact that EPA ignores in its characterization of these studies [USEPA, 1996c, p. 32]. The Agency uses the "similarity" of responses in the summer camp studies and in a single chamber study of heavily exercising children [McDonnell et al., 1985] to adult responses in chamber studies as the basis of their rationale for ascribing adult dose-response functions to children in risk assessments. When corrected, the mean FEV decrement at 0.12 ppm ozone in the summer camp studies is 1.4%, about a third of that attributed to adults. McDonnell et al. (1985) provide additional evidence that children are less sensitive to the effect of ozone than are young adults. When corrected for clean air effects, changes in FEV response measured in 8-11 year old children were about half those measured among 18 - 30 year old adults [McDonnell et al., 1983]. The inclusion of the symptomatic moderate-to-severe pain upon deep inspiration (PDI) health endpoint as one of the three health effects of most concern for children is especially strange given that there is apparently no empirical evidence that children experience these symptoms, as the Agency itself acknowledges [USEPA, 1996c, p. 55]. As a result, risks calculated for FEV decrements in children are high by about a factor of two while PDI risks appear wholly speculative.

Compared to risks assessed from chamber or summer camp studies, uncertainties in analyses based on epidemiological estimates of dose-response are greatly enlarged. Such approaches are confounded by meteorological variables (such as humidity), allergens, other potentially confounding pollutants, and poorly known individual personal exposures. The Agency appears to recognize a number of these difficulties [61 FR 65726]. As noted, even with the lesser reliability of such studies, the proposed standard would reduce projected NYC total asthmatic admissions risks by only 0.6%. This small benefit would be reduced even further if 0.06 ppm rather than 0.04 ppm background ozone risks were taken into account. In addition, EPA's hospital admissions risk model may have inflated admissions risk by applying epidemiological response estimates derived from the peak pollutant period (June-August) to the entire 214 day smog season.

6) Risk model uncertainties provide added evidence that ozone risks are over-estimated.

In the Agency's proposal and ancillary support documents, EPA notes several uncertainties associated with the inputs to its risk model. These include extrapolation of dose-response functions to assumed background levels of 0.04 ppm, assigning to children the same symptomatic response rates as observed for adults, and failing to account for attenuation of responses upon repeated exposure.

Confining the estimation of risk to levels above natural background concentrations is a commendable means of focussing the regulatory effort on effects that can be controlled. However, API questions the choice of the 0.04 ppm ozone background value. Since the proposed standard uses a 3-year average of 3rd highest annual daily maximum 8-hour average values as an attainment measure, a similar statistic should be used as the natural background estimator. Background ozone levels using this statistic range from 0.045 to 0.062 ppm over 1984-1995 across eight remote sites with a median value of 0.054 ppm. Use of a 0.06 ppm O₃ background would thus provide a more realistic estimator of controllable effects. In their recent AWMA paper, Whitfield & Richmond (1996), compute the effect of such a change in assumed ozone background level on modeled FEV decrement $\geq 15\%$ risks for 0.08 ppm/8HR/1EX and 0.08 ppm/8HR/5EX standards. Across the 9 cities, they report a decrease in projected risks of 31% and 18%, respectively.

API also questions whether responses reported for multi-hour exposures at 0.08 and 0.10 ppm would remain statistically significant after correction for responses at 0.06 background levels. Consistent findings of significant effects after multi-hour exposures at 0.08 ppm were a primary reason the Administrator chose to propose an 8-hour, 0.08 ppm ozone standard.

The Agency also consistently fails to account for attenuation of response upon repeated exposures. As discussed earlier, EPA expresses special concern about the frequency of ozone exposures during the smog season. However, repeated exposures, particularly during consecutive days on which alternative 8-hour standard levels are exceeded, result in less response than do single exposures. As discussed in the CD [p. 7-48], responses to 6.6-hour average exposures at 0.12 ppm ozone are reduced on the second consecutive day and have vanished by the third. To the extent that multi-day episodic patterns are typically encountered in non-attainment areas, calculated response magnitudes and frequencies are overestimated in the EPA risk model.

In computing 8-hour risks, Whitfield et al., 1996 develop dose-response functions from EPA chamber studies conducted at a single breathing rate of 40L/minute, roughly comparable to a size-adjusted equivalent ventilation rate (EVR) of 20 L/min/m². However, because the subjects participating in these studies varied in size, their EVRs ranged between 13 - 27. The approximation used by Whitfield over-estimates projected risks, since modeled EVR distributions are strongly peaked at low EVR levels and response rates are decreased at lower ventilation rates.

In summary, there are a number of reasons to suspect that the levels of protection afforded by the current standards are much larger than currently assumed by the Agency. Taken together, the preceding analyses suggest that the quantitative risk assessment used in the proposal likely

overestimates ozone risks to children by over an order of magnitude. If projected for the next most susceptible group identified by EPA, outdoor workers, risks of FEV decrements of $\geq 15\%$, $\geq 20\%$ and PDI would be lower by factors of 4, 10 and 2, respectively, than those projected for children. Risks to the general population who are outdoors and exercise less would be lower still.

Conclusion

Considering the impacts of revision, the Agency should reconsider its action and reaffirm the current primary standard. Should EPA feel compelled to issue a revised standard for non-health reasons, it should be no more stringent than the current standard and of a form that would minimize the implementation burden. This course would bring EPA into agreement with the conclusions of the Clean Air Scientific Advisory Committee, impaneled to evaluate the technical bases of revision, who found that none of the alternative standards under consideration were significantly more protective of the public health. The Agency would also be supported in its reconsideration by the conservatism of existing EPA monitoring and modeling policies as well as recent evidence indicating that levels of protection provided by the current and alternative standards are larger than previously assumed.

Appendix A - Ozone Health Effects: Detailed Comments

Comments on the Environmental Protection Agency (EPA) Health Rationale for Proposed Revised Ozone (O₃) National Ambient Air Quality Standards (NAAQS)

In a December 13, 1996 Federal Register notice (USEPA, 1996a)/[61 FR 65716], the EPA Administrator proposes to change the primary (health-based) NAAQS from the current 0.12 ppm daily maximum 1-hour average value not expected to be exceeded more than once per year on average over a three year period to a daily maximum 8-hour average standard that is attained when a 3-year average of 3rd highest annual values does not exceed 0.08 ppm. As discussed elsewhere in these comments, this revision draws many additional areas into non-attainment and imposes substantial implementation burdens on the States and non-compliance regions.

Considering the impacts of revision, EPA should reconsider its action and reaffirm the current primary standard. Should the Agency feel compelled to issue a revised standard for non-health reasons, it should be no more stringent than the current standard and of a form that would minimize the implementation burden. This course would bring it into agreement with the conclusions of the Clean Air Scientific Advisory Committee (CASAC) impaneled to evaluate the technical bases of revision who found that none of the alternative standards under consideration were significantly more protective of the public health. The Agency would also be supported in its reconsideration by the conservatism of existing EPA monitoring and modeling policies as well as recent evidence indicating that levels of protection provided by the current and alternative standards are larger than previously assumed.

In quantifying the level of protection provided by the proposed standard, the Administrator relies heavily on the table, reproduced below, of projected risks to outdoor children under alternative forms of revised primary standards [61 FR 65725]. EPA concludes that risks for the proposed standard lie between those projected for the 0.08 ppm 8-hour standards with 1 and 5 expected

Table 1 - Percent of Outdoor Children Estimated to Experience Various Health Effects 1 or More Times per Year Associated with 8- and 1-Hour Ozone Exposures Upon Attaining Alternative Standards*

Level	Standard Form	Abbreviation	8-hr ΔFEV _{≥15%}	8-hr ΔFEV _{≥20%}	1-hr PDI
0.07ppm	8-hr, 1 ExEx	07/8HR/1EX	3.0 (1.0-6.6)**	0.4 (0.1-1.8)	0.3 (.01-1.9)
0.08	8-hr, 1 ExEx	08/8HR/1EX	5.1 (2.2-9.6)	1.4 (0.5-3.7)	0.6 (.05-2.7)
	8-hr, 5 ExEx	08/8HR/5EX	6.7 (3.3-11.9)	2.3 (0.8-5.3)	0.8 (0.1-3.2)
0.09	8-hr, 1 ExEx	09/8HR/1EX	7.7 (3.8 [#] -13.3)	2.7 (1.0-6.1)	0.9 (0.1-3.5)
	8-hr, 5 ExEx	09/8HR/5EX	9.5 (5.1-15.9)	3.8 (1.5-7.9)	1.3 (0.2-4.2)
0.12	1-hr, 1 ExEx	12/1HR/1EX	8.3 (4.2 [#] -14.2)	3.0 (1.1-6.6)	1.0 (0.1-3.6)

* Acronyms: ΔFEV = forced expiratory volume decrement in one second; PDI = moderate to severe pain upon deep inspiration; ExEx = annual expected exceedances; 8107 = 8-h, 1 ExEx, 0.07 ppm standard. Estimates aggregate 9 urban areas with 3.1 million children

** 90% credible interval

Apparent transcription errors in original values (3.3, 8.2) corrected upon recalculation [API, 1996]

exceedances [61 FR 65731]. Similarly, EPA concludes that an 8-hour standard, attained when the 3-year average of 3rd highest values does not exceed 0.09 ppm, provides a comparable level

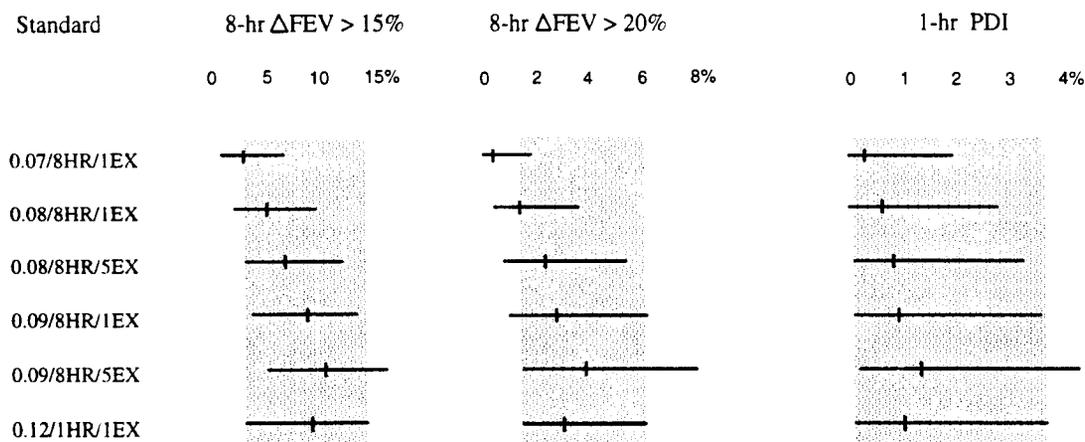
of protection to that projected for the current 0.12 ppm hourly standard [61 FR 65732].

CASAC Conclusions

In reviewing CASAC's conclusions concerning an earlier 1995 version of this table [61 FR 65728; fn 7], the proposal notes that CASAC found "that there is no 'bright line' which distinguishes any of the proposed standards (either the level or the number of allowable exceedances) as being significantly more protective of public health," and noted that the differences in percent of outdoor children responding between the present standard and the most stringent standard "are small and their ranges overlap for all health endpoints. [emphasis added]" Accordingly, the Agency notes that CASAC recognized [61 FR 65727] that "the selection of a specific standard level [within the range of evaluated alternative standard risks] is a policy judgment."

In response to these CASAC findings, the Agency revised the 1995 version of the risk table to include both risk ranges and central tendency point estimates that allow EPA to distinguish among alternative standards. The 1995 relative risk table reviewed by CASAC compared 9-city ranges of the median percent of children responding one or more times per year under alternative standards. The revised 1996 post-CASAC review table published in the proposal compares midpoints of 9-city ranges of median risks as point estimates of median risk and redefines risk ranges to be the 90% credible interval (CI) - the range of midpoints of 5th and 95th centile risk ranges across the 9 cities. As illustrated in Figure 1, although the median risks differ slightly, the

Figure 1 - Median Percent and 90% Credible Interval of Outdoor Children Estimated to Experience Various Health Effects 1 or More Times per Year Associated with 8- and 1-Hour Ozone Exposures Upon Attaining Alternative Standards*



* Acronyms: FEV = forced expiratory volume decrement in one second; PDI = moderate to severe pain upon deep inspiration; 0.07/8HR/1EX = 0.07 ppm standard, 8 hours, 1 expected exceedence. Shaded area = part of alternative standard bracketed by the 0.12/1HR/1EX standard range. Estimates for 9 urban areas with 3.1 million children.

resulting risk range overlaps in the revised 1996 table are even larger than those in the 1995 table with the 90% CI of the current 0.12 ppm, 1-hour, 1-exceedence standard bracketing all median risks but for the most stringent 0.07 ppm, 8-hour, 1-exceedence alternative standard and substantially overlapping their 90% CIs.

In responding to CASAC's conclusion that there would be no significant increase in public health protection resulting from the standard changes under consideration, the Agency gives three arguments explaining its disagreement: that 1) the small differences in median risk are *statistically* significant within cities, that 2) CASAC failed to appreciate that these small differences represented "hundreds of thousands of times that children would likely experience such effects," and 3) that CASAC was confused by differences among cities that obscured differences among standards [61 FR 65728]. As stated in the proposal:

Within any given urban area, statistically significant reductions in exposure and risk associated with functional and symptomatic effects result from alternative 8-hour standards as the level changes from 0.09 ppm to 0.08 ppm to 0.07 ppm. These reductions represent differences of hundreds of thousands of times that children would likely experience such effects under the range of alternative standards considered relative to the current standard.⁷ There are significant uncertainties in such quantitative estimates, however, and there is no break point or bright line that differentiates between acceptable and unacceptable risks within this range.

⁷ With regard to these risk analyses, CASAC concluded "that there is no 'bright line' which distinguishes any of the proposed standards (either the level or the number of allowable exceedances) as being significantly more protective of public health," and noted that the differences in percent of outdoor children responding between the present standard and the most stringent standard "are small and their ranges overlap for all health endpoints." (Wolff, 1995b) To address any apparent differences between EPA's and CASAC's conclusions, it is important to note that EPA's risk analysis report (Whitfield et al., 1996) makes clear that there are *statistically significant* differences in estimated risk for alternative standard levels; whether one judges the differences to be *significant* or *small* can depend on whether one focuses on *percentages*, as CASAC's letter did, or on *total numbers* of times that children or other at-risk individuals experience such effects. The overlap in the ranges of risk referred to in the CASAC letter reflect *differences among cities* used in EPA's risk analysis (e.g., air quality, exposure patterns, environmental factors), *not random uncertainties in risk estimates within any given city*. Thus, the fact that the ranges overlap does not mean that there are no real or statistically significant differences in protection among alternative standards [emphases in the original].

For the reasons discussed below, the arguments cited do not adequately justify a decision to propose and promulgate a revised standard.

The first EPA argument appears to miss CASAC's apparent point that although perhaps distinguishable, the differences in protection afforded by alternative standards were considered small and not medically or clinically significant enough to warrant distinguishing among them. As noted in the proposal, "...some CASAC members and others have suggested that it is difficult to determine if a margin of safety exists for any particular level and therefore, in their opinion, the differences in health protection may not be significant enough to justify a change from the

current standard" [61 FR 65729]. Furthermore, relying on statistical distinctions rather than the magnitudes of the differences may be irrelevant in the case of modeled risk estimates because vanishingly small differences that truly exist between alternative standards can be made *statistically* significant by arbitrarily increasing the number of stochastic runs of the model.

The second EPA argument incorporates a redefinition of the health endpoint that makes the same effect look larger and of potentially more concern by changing the units of measure from the number of people affected to the number of likely effect occurrences within the entire population. However, the number of occurrences per individual is the more relevant measure of health protection. In the Whitfield et al., 1996 risk analysis used to generate the risk table, the dose-response functions used are probabilistic, with only a fraction of those exposed at certain levels responding. By implicitly assuming that the responding population fraction is invariant (i.e., that the same individuals always respond and "sensitive" individuals remain continuously sensitive), and not a measure of temporal response variability within the upper end of the exposed population response distribution, the analyst confines occurrences to a fixed "responder" population. As Whitfield states:

Results discussed so far have focused on the people measure for headcount risks, which addresses the fraction of individuals who may experience a specific health effect one or more times during an ozone season. For this measure, an individual can be counted at most one time. The "person-occurrences" measure counts the number of times in an ozone season that individuals experience a specific health effect. For this measure, an individual can be counted more than one time. Individuals who respond one or more times are called responders. The total number of person-occurrences divided by the number of responders yields an estimate of the number of times on average in an ozone season that a responder experiences a specific health effect. [Whitfield et al., 1996, page 47]

The assumption of constant sensitivity is questionable on several grounds, not the least of which is the Agency's own uncertainty as to whether the "responder" hypothesis is valid. As stated in the proposal, "it is not clear whether these 'hyperresponders' constitute a population subgroup with a specific risk factor or simply represent the upper end of the O₃ response distributions within the general and at-risk populations [61 FR 65722]."

Although there are studies indicating modest response stability among individuals occasionally exposed under identical conditions, studies of repeated exposure suggest, if anything, that it is the "nonresponders" rather than the "responders" that have a reproducible response [Linn et al., 1988]. The numerous studies of temporal response attenuation upon repeated exposure indicate that the constant sensitivity assumption is demonstrably false for "responders". There is also evidence of a temporal ozone sensitivity that may be correlated with hormone-driven fluctuations in breath nitric oxide (NO) concentrations, a potent ozone scavenger [Fox et al., 1993; Kharitonov et al., 1994]. Further evidence of variable sensitivity can be found in the individual response patterns of the EPA clinical studies used as the basis for Whitfield's probabilistic 8-hr population dose-response functions. For example, in Horstman et al., 1990, individual subjects

generally fail to demonstrate a dose-response relationship when exposed to differing ozone concentrations. Among the 21 subjects exposed under quasi-continuous exercise for 6.6 hours to ozone levels of 0.00 ppm, 0.08 ppm, 0.10 ppm and 0.12 ppm, only five exhibited monotonically increasing FEV (forced expiratory volume in 1 second) decrements $\geq 15\%$ with increasing ozone concentrations; two of the remaining 16 subjects reflect a steady improvement in lung function; and 14 reflect varying responses apparently unrelated to increasing ozone concentration. Furthermore, of the six subjects experiencing FEV decrements $\geq 15\%$ at 0.08 ppm, only three achieve or exceed this decrement at exposures of 0.10 ppm and 0.12 ppm. The foregoing evidence suggests that "responders" more likely represent a time-variant upper end of the population O₃ response distribution than a class of constantly sensitive individuals.

The importance of the "responder" assumption to EPA's second multiple exposure argument can be illustrated with Whitfield's risk simulations for the Washington DC area. The percent of outdoor children responding under attainment of the 0.09 ppm/8HR/5 EX and 0.07 ppm/8HR/1 EX alternative standards is 13.4% and 3.6% [page 168]. For the 198,860 outdoor DC children assessed [Johnson et al., 1996b, p. 124], this corresponds to 26,647 and 7159 responders, respectively. Whitfield estimates [page 50] that each DC responder will experience 7.5 and 8 FEV decrements $\geq 15\%$ per year, respectively. The difference in the annual number of population responses between the two standards can be calculated as $26,646 \times 7.5 - 7159 \times 8 = 142,573$. Note however that if the "responder" assumption is false, the number of responses calculated for each standard are distributed instead among the total DC population of outdoor children, 198,860, rather than among the 7159 or 26,646 "responders". The average number of annual responses per child drops then from 7.5 to 8 to $(26,646 \times 7.5 / 198,860 =) 1.0$ to $(7159 \times 8 / 198,860 =) 0.29$, well within the non-adverse "nuisance" effect frequency identified by CASAC [61 FR 65723]. In this case the "hundreds of thousands of times that children would likely experience such effects" is reduced to one or less occurrences per child per year.

In its third argument, the Agency attributes the apparent overlap noted by CASAC in health protection afforded by alternative standards to climatic and demographic differences among cities "(e.g., air quality, exposure patterns, environmental factors)" rather than to differences among standards. The issue is the degree to which these parenthetical parameters predominate the risk overlap since 1) considerable effort was expended by EPA in adjusting air quality distributions to simulate comparable marginal attainment for each city, 2) a common activity database was used for each city, and 3) although differing environmental factors (e.g., temperature) among cities may influence selection of model parameters such as warm-day/cold-day activity or air conditioning status, the secondary impact of these meteorological variables is probably small in contrast to the primary impact on air quality which is normalized during the attainment simulation adjustment to comparable air quality across cities.

One factor that is different among cities is the random number sequence used to select stochastic variables such as specific activity patterns. This factor contributes to the random uncertainty among cities that the Agency suggests confounds CASAC's conclusions. The ten replicate runs of the probabilistic NAAQS exposure model for ozone (pNEM/O₃) used by EPA per city may not sufficiently reduce this source of variability to distinguish among standards. Recent Agency

risk analyses of the proposed standard use synchronized random number generators to eliminate this contribution to city overlaps. The degree to which stochastic uncertainty contributes to city overlap can be evaluated upon EPA's release of this information.

In summary, the reasons provided by EPA for disagreeing with CASAC's conclusion, that little practical improvement in the level of health protection would result from promulgation of the alternative ozone standards under consideration, do not adequately justify its decision to propose and promulgate a revised standard nor to impose the implementation burdens that will ensue.

Increased Levels of Protection

To put its judgements about health effects that are adverse to individuals into a broader public health context, the Agency has used the results of the human exposure and risk assessments to provide a basis for evaluating the acceptability of various levels of residual risk and the adequacy of public health protection afforded by attainment of the current and alternative standards. It is fully supported in this regard by CASAC who concluded that "EPA's risk assessments must play a central role in identifying an appropriate level" for the ozone standard [61 FR 65727]. Although the risk estimates tabulated in the proposal are subject to uncertainties, the Agency believes that they do represent reasonable estimates and the state of the art given the available information [61 FR 65724-5].

In proposing a revised standard, the Administrator identifies, as acceptable, associated risks quantified in the risk table. API has reviewed EPA's risk assessment approach and finds a number of reasons to believe that existing standards provide greater levels of protection than currently assumed. These include overestimates of human exposure that result from conservative monitoring and modeling policies not explicitly considered in the risk assessment and suspect methodologies present in key health effects studies used by the Agency to quantify risk. These lowered risk findings would support an EPA reevaluation of the need to promulgate revised standards.

o Personal Ozone Exposures

The ozone probabilistic NAAQS Exposure Model (pNEM/O3) is an integral part of the EPA risk assessment that forms the basis of the proposed standard. Although under active development and use over the past decade, pNEM/O3 has never been validated. API recently conducted a 1995 pilot study of personal ozone exposures in the Los Angeles basin [Johnson et al., 1996a]. A comparison of monitored personal exposures to those predicted by pNEM/O3 indicated that the current model estimates of ozone exposure concentrations exceed the monitored values. Mean ratios of monitored to modeled personal exposure concentrations to ambient ozone levels ranged from 0.5 to 0.6. This study suggests that pNEM/O3 simulations used in the O3 risk assessment approximately double actual O3 exposure levels. A number of possible reasons for such overestimates are discussed below.

o Fixed-site Ambient Monitor Interferences and Vertical Gradients

As discussed in the ozone Criteria Document (USEPA, 1996b)/[CD], current network O₃ monitors are subject to a number of interferences that bias upward reported ozone values [CD 3-90, 3-96]. Recent studies [Leston & Ollison, 1993; Hudgens et al., 1994] document humidity effects in ethylene-chemiluminescence monitors ranging up to +18% and polar aromatic compound interferences in ultraviolet (UV) absorption monitors ranging up to 40 ppb. EPA staff generally discourage State and local monitoring agency attempts to correct for these effects [Leston & Ollison, 1993]. Accordingly, the pNEM/O₃ exposure model uses uncorrected monitoring data as reported to the Aerometric Information Retrieval System (AIRS) database and likely overestimates peak exposures and risks to a similar degree in model simulations.

The Agency also fails to propose modifications to 40 CFR Part 53 to provide wet calibration protocols for use in minimizing water vapor interferences as recommended in the Criteria Document [CD, 3-91]. The American Society for Testing and Materials (ASTM) also notes that wet span tests are necessary to detect anomalous ozone scrubbers and correct negative bias in UV instruments from poisoned MnO₂ cartridges [ASTM, 1996]. The Agency should also use this opportunity to update the vintage performance specifications in 40 CFR Part 53 concerning interference testing requirements and equivalent methods specifications. Interference test requirements should be updated to include the newly reported interferants discussed in the CD and these tests should be conducted in the presence of water vapor and ozone, since for a number of compounds [Leston & Ollison, 1993], the interference effect is inoperative in the absence of humid ozone. Currently the UV equivalent method is approved for use with up to 0.06 ppm in total interferant bias with respect to the chemiluminescence Federal Reference Method. Most of the quantified interferences [ASTM, 1996] are polar aromatic compounds whose concentrations are not routinely monitored and so not available to correct ambient UV ozone measurements. This results in an ambient O₃ measurement uncertainty of up to 75% of the proposed 0.08 ppm standard level that should be reduced by at least half. In its review of the UV ozone method, ASTM, 1996 concludes that " the interference sensitivities may limit its use for ambient and workplace atmospheres...if interferences are suspected, it is preferable to use another test method."

A new possible bias in ambient UV ozone monitors and the National Institute of Standards & Technology (NIST) UV ozone calibration standard is suggested by recent publications exploring O₃ photolysis kinetics near 254 nm, the probe wavelength used to quantify O₃ in these instruments. Reported findings suggest that ozone levels within the instruments may be increased by photolysis during the measurement process. Flynn et al., (1996) report a newly discovered reaction between vibrationally ($\nu \geq 26$) excited molecular oxygen (O₂), produced from photolysis of O₃ at 248 nm, and normal O₂. This efficient process produces an branching chain reaction [O₂ ($\nu \geq 26$) + O₂ = O₃ + O; O + O₂ + M = O₃ + M] capable of regenerating three new O₃ molecules from each O₃ molecule photolyzed. Since collisional relaxation of excited O₂ ($\nu \geq 26$) prior to reaction with O₂ by the other air molecules tested [nitrogen, carbon dioxide, and nitrous oxide] is relatively slow, autocatalytic production of ozone within the sampling cells of ambient UV ozone monitors and NIST calibration standards may occur during

measurement. This mechanism might in part account for the tendency of UV monitors to report higher peak ozone levels than collocated chemiluminescent instruments [Leston & Ollison, 1993].

Current EPA ambient monitor siting guidance may also contribute to overestimates of personal ozone exposure. Present guidelines direct that ozone monitor inlets be installed 3 to 15 meters above grade. Recent studies of vertical ozone gradients indicate that ozone concentrations frequently increase with height above the ground [Trotter et al., 1996], due perhaps to ozone surface deposition and emissions of ozone scavengers such as isoprene (e.g., human breath and vegetation) and NO (e.g., soil, human breath, and auto exhaust) near the surface. Recently measured increments in ozone levels between 2 and 10 meters averaged 13% [Wisbith et al., 1996]. The current pNEM/O3 model does not correct for this effect and so may overpredict ozone exposure accordingly.

o Exposure Modeling Uncertainties and Assumptions

In the proposal [61 FR 65724] and ancillary support documents, EPA enumerates uncertainties associated with pNEM/O3 model inputs. The Agency notes that a "key uncertainty in model inputs results from the availability of only a limited human activity database, with regard to both the number of subjects who contributed daily activity diary data and the short time periods over which subjects recorded their daily activity patterns". Although the proposal points to a "repeated activity" uncertainty (discussed below in these comments) that stems from such sparse data, it fails to note a more egregious approximation that results from the subsetting of these data to identify activities of "outdoor children".

Johnson et al., 1996b [p. 105] list three criteria leading to the selection of specific subject activity days as characteristic of outdoor children: at least one winter weekday diary day with more than 2 hours outdoors; or at least one winter weekend with more than 3 hours outdoors; or at least one summer (June-August) weekday or weekend with more than 4.5 hours outdoors. Activity-days from children meeting one of these criteria are then collected into a separate outdoor child database from which annual sequences of daily activities were compiled stochastically.

The difficulty with this approach is best illustrated with the California time/activity database which supplies 311 of the 479 subjects in the "outdoor children" database [p. 106]. About 60% of the available subjects fail to meet the outdoor child criteria [p. 122]. Since each child in the California database reports only a single activity day, by eliminating the non-outdoor children in this data set a resulting annual sequence of activity days from this subsetted source ensures that every "outdoor child" spends over 2 hours outdoors on every winter weekday, spends 3 hours outdoors on every winter weekend day and spends over 4.5 hours outdoors on every summer day. This is clearly a gross distortion of likely individual activity patterns and is probably a key reason that exposures of "outdoor children" are so much higher than for other population groups.

The Cincinnati database supplies 130 of the 479 subjects but reports three activity days per child. The inclusion of at least some "non-criteria" days from this database mitigates the above

distortion but still ensures that annual sequences of activity days of subjects from this subsetted source spend over 120 days/year meeting the outdoor child criteria. Even if only one activity day per individual meets the outdoor child criteria in the total EPA database [p. 106] for this cohort, "outdoor children" will spend over 220 days/year in daily activity patterns meeting these criteria. The EPA exposure assessment attributes such behaviors to about 40% of the total child population, a likely gross overestimate of exposure and concomitant risk.

As discussed earlier in these comments pNEM/O3 has not previously been validated against field measurements of population exposure. Neither has it undergone substantial sensitivity testing for variations in model inputs. The current version of pNEM/O3 fails to account for several effects that may influence personal exposures: reductions in ambient ozone by automotive exhaust NO in the near roadway and in-vehicle microenvironments [Johnson et al., 1995]; open windows in non-residential buildings; repetitive weekday activities; and commuting activities of children. The current model also incorporates a number of questionable assumptions such as treating the entire population as "motivated exercisers" and increasing all hourly ambient monitoring values by 6% to simulate personal exposure. In coordination with EPA staff, API has modified the pNEM/O3 model to account for missing variables and explored the quantitative impact of several assumptions [Johnson, 1996]. The net effect of these modifications is a more realistic version of pNEM/O3 that projects substantially reduced population exposures compared to the EPA version used in the proposal.

In sensitivity tests of the model, use of random number generator synchronization greatly reduces stochastic noise in the calculation. Differences in computed values thus arise solely from

Table 2 - Ratios of Modified Model to Standard pNEM/O3 Model Median Numbers of Outdoor Workers Experiencing 1-Hour Exposures with Ozone > 120 ppb and EVR# > 30 and 8-Hour Exposures with Ozone > 80 ppm and 13 < EVR < 27 - Los Angeles (1991)

Test Parameter - 6 pNEM/O3 runs	1-Hr Exposures	8-Hr Exposures
*In-Vehicle and Roadside Exhaust NO Ozone Reduction Added	0.97	0.93
*Arm Work effects on Estimated EVR Added	0.95	0.85
Normal Exercisers Only	0	0.76
Non-Commuters Only	1.02	0.90
*O3 Monitor Inlet Height Adjustment Added	0.99	0.93
*Non-residential Building Windows Opened	1.00	1.00
Repetitive Activities Added	0	0.03
*Deleted 6% Increase in O3 Monitoring Values	0.89	0.79
Motivated Exercisers Only		
Composite of Starred (*) Variables - 6 pNEM/O3 runs	0.83	0.44
Composite of Starred (*) Variables - 10 pNEM/O3 runs	0.73	0.41
Normal Exercisers Only		
Composite of Starred (*) Variables - 6 pNEM/O3 runs	0	0.38
Composite of Starred (*) Variables - 10 pNEM/O3 runs	0	0.31

EVR = equivalent ventilation rate = L/minute/m² body surface area (BSA)

changes in the model algorithms and input data. However, for one parameter, repetitive activities, random number generators could not be synchronized since different numbers of random numbers were required for each version of the model. This resulted in more variable comparisons for this parameter. The sensitivity of the model to changes in individual parameters for the Los Angeles outdoor worker cohort is tabulated below. As compared to the standard pNEM/O₃ model used in the proposal, parameter changes making the model more realistic resulted in reduced projected exposures for outdoor workers. Although not specifically tested, comparable reductions would be expected for model runs using the outdoor children cohort.

Because of the relatively high breathing rates (EVR > 30) required to experience effects at 1-hour exposures to 0.12 ppm O₃, the assumption that 100% of the population are "motivated exercisers" is particularly extreme. Few if any normal exercisers will maintain these breathing rates, about 60 L/min for an adult, continuously for an hour. Perhaps only a third of the adult (> 21 years old) and half of the adolescent (12-21 years old) population is fit enough to maintain these ventilation rate levels with any frequency, even if "motivated" [USHHS, 1996]. This "100%" assumption is further contradicted by direct observational studies of children under free-ranging, natural conditions in southern California. Bailey et al., 1995 indicate that 6-10 year old children spent only 3.1% (18 minutes) of their observed time between 8 am and 8 pm in high intensity activities lasting, on average, 6 seconds each (95% lasting < 15 seconds). Thus even if fit enough, few children apparently wish to expend this level of effort for such prolonged durations.

The ventilation rates modeled for the 8-hour standards are relatively lower and the effect of the 100% motivated exerciser assumption is less extreme. However, probably even fewer individuals will maintain quasi-continuous (50 minutes/hour) exercise in the 13 < EVR < 27 range (about 25-55 L/min for adults) for 8 consecutive hours. As a result only a very small fraction of the effects projected in Table 1 for the current and alternative standards may actually occur.

For median estimates of exposure, the current model's failure to account for repetitive activities probably increases projected exposure and risk; however, as mentioned above, random number synchronization could not be accomplished for this parameter and the test is particularly noisy. For example, mean estimates of exposure indicate the reverse, that failure to include repetitive activities underprojects exposure and risk. In any event, whether summer activities for children would be as repetitive as for adults is questionable and the practical effect of repetitive activities on summer exposures of children may be small.

The composited impacts of other tested variables on projected exposures are also considerable, as presented in Table 2 for six and ten run averages of pNEM/O₃. Hourly exposures accounting for these lesser parameters in motivated exercisers are overestimated by about 25% and 8-hour exposures by about 60%. For normal exercisers few if any achieve these hourly exercise levels and 8-hour exposures are overestimated by about 65%. Thus the combined effects of model improvements and questionable assumptions indicate that exposures predicted by the current version of pNEM/O₃ may be overestimated several-fold.

It is also interesting to consider whether the reduced exposures resulting from use of a more realistic version of pNEM/O3 would reduce projected risks proportionately. Johnson, 1996 tests this proportionality for outdoor worker FEV/PDI risks using Los Angeles 1991 "as is" air quality and the improved pNEM/O3 model described in Table 2. Table 3 presents the ratio of the fractional change in risk divided by the fractional change in exposure (elasticity) of various health endpoints that can be used to judge the *relative* effects of an improved pNEM/O3 model on projected 1-hour and 8-hour risks. The results indicate that, as compared to an improved version, the current EPA pNEM/O3 model overestimates the number of workers experiencing one or more 1-hour FEV decrements ≥ 15 or 20% per year by factors of 1.37-1.56, underestimates 8-hour FEV decrements by factors of 0.76-0.86, underestimates 1-hour PDI effects by a factor of 0.65, and overestimates 8-hour PDI symptoms by a factor of 1.16. Consequently for this reason and others discussed above, risks derived from these exposure estimates and tabulated in the proposal are overestimated and levels of protection afforded by existing standards may substantially exceed those anticipated by the Administrator.

Table 3 - Mean Elasticities of FEV and PDI Health Endpoints for Numbers of Outdoor Workers Experiencing Health Effects 1 or More Times per Year Associated with 1- and 8-hour Exposures*

Endpoint	Exposures	Elasticity
Δ FEV $\geq 15\%$	1-hour	1.37
	8-hour	0.75
Δ FEV $\geq 20\%$	1-hour	1.56
	8-hour	0.86**
PDI	1-hour	0.65
	8-hour	1.16**

* Acronyms: Δ FEV = forced expiratory volume decrement in one second; PDI = moderate to severe pain upon deep inspiration.

** Not statistically different from 1.0 ($p > 0.05$).

Risk levels assigned to the proposed standard and judged acceptable are already provided by existing regulations.

o Risk Model Uncertainties and Assumptions

In the proposal [61 FR 65726] and ancillary support documents, EPA notes several uncertainties associated with the Ozone Risk Assessment Utility System (ORAMUS), the model used to estimate population risks from exposure model inputs. These include extrapolation of dose-response functions to assumed background levels of 0.04 ppm, assigning to children the same symptomatic response rates as observed for adults, and failing to account for attenuation of responses upon repeated exposure.

Confining the estimation of risk to levels above natural background concentrations is a commendable means of focussing the regulatory effort on effects that can be controlled. However, choice of the 0.04 ppm O3 background value is questionable. This value appears to

have been chosen from 7-month (April-October) averages of 7-hour daily average values at Theodore Roosevelt National Park over 1984-1986, a location thought representative of 8-hour averages at other clean sites in the U.S. [CD, 4-96]. Since the proposed standard uses a 3-year average of third highest daily maximum 8-hour values as an attainment measure, comparisons to a similar statistic, rather than a 7-month average, should be used as the natural background estimator. Twenty-five 3-year averages of annual third-highest daily maximum 8-hour O₃ averages (computed from data provided to EPA [API, 1995]) in eight national parks over 1984-1995 range from 0.045 to 0.062 ppm with a median value of 0.054 ppm. Use of a 0.06 ppm background level in risk calculations would therefore provide a more realistic estimator of controllable effects. In their recent paper Whitfield & Richmond, 1996 report that the effect of such a change in assumed background level from 0.04 to 0.06 ppm on estimated risks was a 31% decrease in FEV decrement $\geq 15\%$ risk averaged across the nine cities for the 8-hour, 1 ExEx, 0.08 ppm standard and a mean 18% decrease for the 8-hour, 5 ExEx, 0.08 ppm standard. The estimated risk decrease for this health endpoint under the proposed standard would be about 25%.

In human chamber studies, ozone associated responses are determined as the differences between responses to fixed ozone concentrations and clean air responses at 0.00 ppm O₃, rather than as differences from background control levels of 0.04 or 0.06 ppm O₃. Although Whitfield et al., 1996 correct their derived dose-response functions for extrapolated responses at 0.04 ppm background levels, it is difficult to validate the magnitude of such a correction since no non-zero ozone exposures have been reported below 0.08 ppm.

In describing their 8-hour EPA exposure pattern study, Hazucha et al., 1992 note that

In both [constant and triangular] O₃ exposures, there was an unexpectedly large mean decrement ($\approx 3\%$) in both FVC and FEV₁ at the end of the first hour of exposure. It was particularly surprising to find such a decrement in the triangular profile, because O₃ concentration at the end of the first 30 minutes of exercise reached only 0.03 ppm, and at the end of the subsequent 30 minute rest period, when lung function was measured, the concentration was still only 0.06 ppm. A somewhat similar pattern of response has been reported by others [Folinsbee et al., 1988].

In the absence of confirming measurements it is difficult to credit the apparent magnitude of these reported 1-hour responses to 0.03-0.06 ppm O₃ exposures; however, an alternative explanation may be that such responses reflect in addition to background responses also effects of exposure chamber artifacts specific to the EPA Chapel Hill facility as discussed in more detail below. Hazucha's results do suggest that background responses may be non-zero and so corroborate Whitfield's correction. The median dose-response curve in Figure B.28 of the Whitfield report projects that 8.5% of the exposed population will experience FEV decrements $\geq 15\%$ at 8-hour exposures to 0.06 ppm with an apparent a zero response threshold at 0.043 ppm. Projected response rates at 0.08, 0.10, and 0.12 ppm are 18%, 28%, and 38%, respectively. A 0.06 ppm background response thus represents about 20% of the projected response rate at 0.12 ppm.

Given a non-zero response at background levels, it becomes questionable whether the functional and symptomatic responses reported in the EPA 6.6-hour studies for 0.08 or 0.10 ppm O₃ exposures would remain significantly different from the 0.06 ppm O₃ background responses. Should these studies fail to report statistically significant responses after appropriate background response corrections, the Agency would lose the scientific core of its proposal since "health effects evidence consistently reporting effects at 0.08 ppm and above for 6-8 hour exposures was a very important factor in the Administrator's decision to propose the 0.08 ppm, 8-hour standard level" [Richmond, 1997]. Considering the burden of implementation imposed by promulgation of the proposed standard, the Agency should postpone promulgation of its proposal until the question of whether 6.6-hour, 0.08 ppm exposure responses significantly differ from 0.06 ppm background responses has been determined.

The inclusion of the symptomatic PDI (moderate-to-severe pain upon deep inspiration) health endpoint as one of the three health effects of most concern for children is especially strange given that there is apparently no empirical evidence that children experience these symptoms. As the Agency acknowledges [USEPA, (1996c), p. 55]:

Based on the available data, it appears that children respond to low-level O₃ exposures in a manner comparable to that of young adults, albeit without symptoms, while older persons exhibit a decreased sensitivity relative to young adults (CD, Sec. 9.6). The lack of symptoms in children and reduced sensitivity in the elderly could lead to an increased risk of an individual receiving a higher O₃ dose. This increased risk of O₃ exposure and dose is a direct result of children and the elderly not taking mitigating behavior to avoid exposure because they do not experience respiratory symptoms; however, this hypothesis has not been tested and has not been demonstrated at this time [emphasis added].

As a result, risks calculated for the PDI health endpoint in children appear wholly speculative.

Almost as curious is the Agency's failure to account for attenuation of response upon repeated exposures. As discussed earlier, EPA emphasizes its special concern about repeated O₃ exposures during the smog season. However, repeated exposures, particularly during consecutive days on which alternative 8-hour standard levels are exceeded, result in less response than do single exposures. As discussed in the criteria document [CD, p. 7-48], group mean responses to 6.6-hour average exposures at 0.12 ppm O₃ are reduced about 30% on the second day and have vanished by the third. To the extent that multi-day episodic patterns are typically encountered, calculated response magnitudes, frequencies, and risks are overestimated in the EPA risk model from a failure to account for response attenuation.

Additional assumptions in the ORAMUS model also merit concern. These include exclusion of non-EPA chamber data from the 8-hour dose-response function derivation, use of artificial chamber subject dosing profiles, attribution of adult responses to children, and application of dose-response functions determined at equivalent ventilation rates (EVR) of 20 L/min/m² BSA to exposures with EVRs ranging from 13 to 27 L/min/m² BSA.

In estimating risks the ORAMUS model uses only dose-response functions derived from Agency studies conducted in the EPA chamber facility in Chapel Hill, NC. While as a set, these studies do provide the most subjects for analysis, functions derived from results measured in this particular exposure chamber produce substantially higher responses and lower effect thresholds than those from other chambers. The Agency argues that there are enough protocol differences in non-EPA studies to preclude pooling them with EPA data [USEPA, 1996c, pp. 107-111].

For example, the 1-hour FEV decrement $\geq 15\%$, heavy exertion, dose-response function derived from the Kulle et al., 1984 study indicates a 10% response rate at 0.24 ppm O₃ with an apparent 0.16 ppm zero response threshold whereas the McDonnell et al., 1983 EPA study projects a 10% response rate at about 0.18 ppm and a threshold of about 0.12 ppm [Whitfield et al., 1996, pp. 103 & 106]. Agency studies used to determine the 8-hour dose-response functions in 18-33 year olds from 6.6-hour exposures (50 min/hr at 40 L/min; 10 min/hr at rest; FEV measured hourly during rest period) report group mean FEV decrements of 13-15% at 0.12 ppm and 7-8% at 0.08 ppm. In comparison, Horvath et al., 1991 predicts a 2% FEV decrement in 30-43 year olds at 0.08 ppm after 6.6 hours and Linn et al., 1994 report group mean FEV decrements at 31 L/min in 22-41 year olds of 2% [CD, 7-54] to 4% [Linn et al., 1994] at 0.12 ppm. Interestingly, an EPA 8-hour 0.12 ppm O₃ exposure study using different O₃ dosing patterns (30 minutes/hr at 40 L/min; 30 minutes/hr at rest; FEV measured at end of rest period) reports mean FEV decrements in 20-35 year olds of 5% after 8 hours [Hazucha et al., 1992]. Even though Hazucha's 6-hr O₃ doses are only about 80% of those in the other 0.12 ppm 6.6-hr studies and hourly FEV response measurements after each 30 minute exposure are delayed by 30 minutes (allowing partial FEV recovery), subject responses in Hazucha's EPA chamber study still exceed the 2-4% responses reported from non-EPA chambers.

Adams et al., 1997 recently completed a series of 6.6-hour facemask exposures to 0.12 ppm O₃ in twelve 20-25 year old subjects. Exposure protocols included a repetition of the 6.6-hour EPA exposure pattern (Folinsbee et al., 1998 and Horstman et al., 1990), triangular diurnal O₃ concentration patterns averaging 0.12 ppm over 6.6 hours similar to Hazucha et al., 1992, and variable breathing rate patterns averaging about 40 L/min over 6.6 hours. Table 4 compares the 0.12 ppm O₃ responses from Folinsbee and Horstman, key studies used in the EPA ozone risk assessment, to those of Adams. Since Adams et al., 1997 make some effort to match the EPA protocols with respect to age, O₃ concentrations, breathing rates, and breathing rate patterns, they come closer to matching the group mean response rates of Folinsbee and Horstman than do the previous efforts by Linn et al., 1994 and Horvath et al., 1991. However, the Adams group mean FEV decrement of about 11% for Exposure Pattern #1, which most closely matches the Folinsbee/Horstman protocol, is still below their 13-15% group mean responses.

More importantly, the fraction (25%) of Adams' subjects with FEV decrements $\geq 15\%$ is only about half that reported (50% combined) by the EPA researchers. This is the more relevant test because it is the fractional response rate that is used in the EPA risk assessment to generate dose-response functions. In fact, the observed response rate at 0.12 ppm for the FEV₁ decrement $\geq 15\%$ endpoint from the combined Folinsbee and Horstman studies was judged to be unreasonable and ultimately not used by Whitfield et al., 1996 [page 33] in developing this dose-response

Table 4 - Comparison of Pulmonary Function Decrements Corrected for Clean Air Responses in 6.6-hour Exposures to 0.12 ppm Ozone*

Study	Number of Subjects (Age)	Group Mean Δ FEV	Number (%) of Subjects with Δ FEV \geq 15% Δ FEV \geq 20%	
Folinsbee et al., 1988	10 (18-33)	14.8%	6/10 (60%)	2/10 (20%)
Horstman et al., 1990	21 (18-32)	13.1	9/21 (43%)	6/21 (29%)
Adams et al., 1997	12 (20-25)			
Exposure Patterns				
#1 - constant O3; constant EVR		10.9	3/12 (25%)	2/12 (17%)
#2 - NJ diurnal O3; constant EVR		10.4	3/12 (25%)	1/12 (8%)
#3 - CA diurnal O3; constant EVR		14.1	6/12 (50%)	3/12 (25%)
#4 - constant O3; variable CW EVR		14.6	4/12 (33%)	4/12 (33%)

*Acronyms: Δ FEV = forced expiratory volume decrement in one second; EVR = equivalent ventilation rate in liters/minute; O3 = ozone; NJ = obtuse triangular diurnal O3 pattern (0.11-0.13-0.11 ppm); CA = acute triangular diurnal O3 pattern (0.07-0.16-0.10 ppm); CW = variable construction worker EVR pattern. Clean air corrections according to Whitfield et al., 1996, Appendix A.

regression in the EPA risk assessment. As a result, Whitfield et al., 1996 project a 38% response rate for Δ FEV decrements \geq 15% during 6.6-hour 0.12 ppm exposures, midway between the Adams and combined Folinsbee/Horstman values. Failure to account for the differing results from other research facilities biases risk estimates high and further underestimates the level of protection provided by the current standard.

A caveat to the above discussion of the twelve-subject Adams et al., 1997 study is that although results from exposure patterns 1-4 were significantly different (paired t-test with Bonferroni correction) from the clean air exposures, they were not significantly different ($p > 0.05$) from each other. However, Whitfield et al. encounter a similar situation interpreting the dose-response information reported by Horstman et al., 1990. The 0.08, 0.10 and 0.12 ppm treatments in that study are significantly different from clean air exposures but only the 0.12 ppm result differs from the 0.08 and 0.10 results, which do not differ from each other. Moreover, as mentioned above, Whitfield et al., throw out the 0.12 ppm FEV \geq 15% data as unreasonably high and proceed to use the 0.08 and 0.10 ppm response data in establishing a dose-response function. In the same spirit, the Adams et al. response rate ratios are used above and subsequently in these comments without further regard to the lack of statistical difference among the group mean decrements.

o Exposure Chamber Artifacts

One reason that subject responses in EPA exposure chamber studies may be higher than in other research facilities is the possibility that artifact irritants are contained the synthetic exposure atmospheres generated for such research. Increasing circumstantial evidence in support of this hypothesis has been presented to CASAC over the past decade [API, (1985); API, (1994)]. In

response, CASAC members have repeatedly asked that a discussion of this issue be included in the Criteria Document [USEPA, 1995a,b]; however, the Agency has refused to honor their request. A brief discussion of this hypothesis is provided below.

Ozone is produced in ambient air from solar (290-700 nm) photolysis of trace ozone precursor pollutants such as NO₂, HONO and aldehydes in the presence of organic species. However, controlled human health effect studies generally use synthetic exposure atmospheres. Chamber studies generate ozone directly by dissociating molecular oxygen in high voltage corona discharges or by photolysis with hard (185 nm) ultraviolet radiation. These more severe ozonization processes also degrade water vapor and volatile organic species present in ozonizer inlet air, potentially both enhancing levels of oxygenated organics as well as producing new species not encountered in ambient air. The question is whether potential ozonizer artifactual irritants are present in chambers at sufficient levels to elicit effects currently attributed to ozone.

Of particular interest in answering this question is the Avol et al., 1984 article that compares responses of chamber subjects exposed to ambient polluted air drawn into the chamber (mean ozone level of 0.153 ± 0.025 ppm) to their responses in synthetically ozonized chamber air (mean ozone level of 0.162 ± 0.002 ppm). Although not significantly different, measured pulmonary function decrements tended to be greater for ozonized air than for the ambient air. However, total irritant symptom scores were significantly enhanced in ozonized air. Avol et al. attribute the unexpectedly reduced irritancy of ambient air to possible copollutant antagonisms, marginally lower subject exercise levels and the higher deviation of ozone concentrations during ambient exposures.

In Whitfield et al., 1996, dose-response curves of Avol et al., 1984 were compared to those from the similar studies of McDonnell et al. (1983) and Kulle et al. (1985). There were substantial differences in thresholds and magnitudes of response among subjects in these studies. Differences between Avol and McDonnell/Kulle might have been expected on the basis of Avol's continuous exercise regimen and potentially attenuated responses from his Los Angeles subjects due to relatively high local ambient levels. However, the substantial differences between the McDonnell's North Carolina subjects and Kulle's Maryland subjects, who all used the same intermittent exercise protocols, were not expected. The 1989 ozone staff paper [USEPA, 1989, pp. VII-10 to 12] addresses these differences by referring to 1) the small number (20-50 at any given exposure level) of subjects tested in each study, 2) the fact that subjects were not selected through population based sampling and 3) the fact that fitted dose-response functions were empirically rather than biologically based. An alternative explanation for the unanticipated differences may be the presence of ozonizer artifact irritants in the Avol mobile Rancho Los Amigos (RLA) and McDonnell EPA chambers that were absent in the Kulle University of Maryland (UMD) facility.

Several characteristics common to the EPA and RLA chambers indicate a higher potential for artifact formation than in the UMD facility. First, both Avol and McDonnell chambers use UV ozonizers that irradiate moist makeup air containing ambient levels of volatile organic compounds (VOC). The Kulle chamber ozonizes dry high purity cylinder oxygen that is titrated

into the main chamber airflow, as do Adams et al., 1997 discussed above. Earlier analysis of ozonizer properties [API, 1985] indicated that elevated hydroxyl radical (OH) levels (1,000-10,000 fold higher OH levels than encountered in the ambient air) would be generated in a UV ozonizer using moist inlet air. Such OH concentrations are capable of significantly degrading VOC species present in ozonizer input gases. Makeup air treatment processes in these chambers are generally ineffective in removing ambient VOC [API, 1985]. The recent summary [Tilton et al., 1994] of EPA chamber air monitoring results [Bufalini et al., 1986; Gay et al., 1987] supports an artifact production hypothesis and demonstrates qualitative trends towards decreasing chamber VOC levels and increased carbonyl (VOC aldehydes & ketones) concentrations with increasing severity of ozonization. In contrast, ozonization of dry, high-purity cylinder oxygen in the UMD facility should provide substantially less chance of potential artifact formation.

Second, both RLA and EPA chambers recirculate 80-85% of the chamber air. Organic species generated in the ozonizer or emitted by subjects into the chamber have a greater tendency for accumulation than in the UMD chamber where airflow is once through with no recirculation.

Finally, the EPA Chapel Hill, NC facility appears to have a unique, additional source of potential chamber irritants. Until about 1989, steam used to rehumidify dried EPA chamber makeup air contained a volatile amine, N,N-diethyl aminoethanol (DEAE), added to reduce carbonic acid corrosion of steam pipes by steam condensate. This precautionary practice was commonly used in humidity control systems until linked with employee "sick building syndrome" complaints [Munk, 1988]. This tertiary amine has irritant properties with complaints of dermatitis, headaches, respiratory irritation and chest tightness from employees where DEAE was used in the humidification system. Although published airborne DEAE measurements [Edgerton et al., 1989] have been low (0.6-10 ppb) with respect to OSHA occupational standards (10 ppm TWA₈), individuals may become sensitized with allergic reactions of rhinitis or asthma at low exposures [Iglewicz & Pellegrino, 1987]. We are unaware of any DEAE measurements made within the EPA facility. Gas phase reaction rates of DEAE with ozone are thought to be slow [Gay, 1988] with wall deposition the primary fate [Edgerton et al., 1989]. For example, ozonization rates, producing formaldehyde and (CH₃)₂NCHO for a similar compound, trimethylamine, approach 10⁻¹⁷ cc/molecule-seconds [Atkinson & Carter, 1984]. Potential heterogeneous ozonization rates of DEAE on chamber surfaces are unknown; however, ammonia from hydrolysis of accumulated DEAE on chamber surfaces may be released over time [Gay, 1988].

The recent reconnaissance surveys of EPA chamber atmospheres [Tilton et al., 1994] report elevated peroxide and carbonyl levels that increase and chamber VOC levels that decrease with ozonization severity. Since incremental peroxide enhancements were only a percent of ozone increases (reaching 5 ppb as a maximum), these artifact species are probably inconsequential. Incremental carbonyl levels were more substantial (10-60 ppb). However, interpretation of the carbonyl results is complicated by both potential positive and negative measurement errors. On one hand, Smith et al., 1989 find that ozonization products of the carbonyl reagent, 2,4 dinitrophenylhydrazine (DNPH), may not be chromatographically resolved from aldehyde-DNPH derivative peaks under all conditions and may also produce apparently new aldehyde

species (i.e. possibly the x-acetaldehyde in Bufalini & Gay, 1986). On the other hand, Arnts & Tejada, 1989 report that ozone degrades carbonyl-DNPH derivative species used to quantify gas phase aldehyde concentrations. The Arnts & Tejada results suggest that it is more likely that differential carbonyl values reported by Tilton et al., 1994 may be underestimated by factors of 2-4 due to this ozone interference. Corrected carbonyl levels might range from 20-240 ppb as a result. The carbonyls can be viewed as surrogates for the additional polar oxygen- and nitrogen-containing VOCs produced in the ozonizer but not assessed by EPA staff. Cumulative levels of these latter species could potentially exceed those of the carbonyls. As Tilton et al., 1994 conclude:

It should be emphasized that the concentrations of carbonyl compounds observed in this study may represent the lower bounds of possible production during ozonation...whether carbonyl compounds occur in sufficiently high concentrations to affect any of the results obtained from controlled exposures to ozone over the range of 120 to 500 ppb ozone in [the EPA facility] or in similar exposure facilities is a question to be examined by the health researchers. The occurrence, however, of carbonyl compounds as the result of ozonation of ambient air indicates that careful engineering design and quality control measures should be observed in all human and animal exposure chambers, including an examination of the composition and chemistry of the atmospheres introduced into the exposure chambers...it should be pointed out that EPA has built a new controlled-exposure facility and the [present EPA] exposure chambers will no longer be used once the new facility is fully operational.

Tilton et al. also note that between their 1987 and 1993 surveys of the exposure chamber facility, "the air train intake port was moved from the side of the building (2 meters above the ground) to the roof of the one-story building". This action was in response to recommendations in reports from the earlier 1985 and 1987 surveys [Bufalini et al., 1986; Gay et al., 1987]. The chamber intake port was also within 2 meters of vehicles stopped or standing in the parking lot abutting this side of the facility. As noted by EPA survey staff:

During an initial visit to the facility on December 3, 1985, a quick tour was given of the exposure chamber and its operation. It was noted that the intake air port was on the side of the facility relatively near to a parking area for four to six vehicles and faces an access road across to UNC's maintenance shops. Under certain conditions we suspect that air drawn into the intake will contain vehicular and other emissions. ... Since researchers at the [exposure chamber] facility have noticed vehicular exhaust odors within the facility at certain times, consideration should be given to putting in vent stacks to bring the incoming air in from a higher level above the building. [Bufalini et al., 1986]

When the first chamber study was undertaken in December of '85 there was a greater motor vehicle activity near the facility. In fact, a number of large delivery trucks and an electric pole maintenance truck with engines running were close to the building. The exhaust fumes from these vehicles could be noticed inside the chamber facility by their odor. During the April 22nd sampling period there were only four or five vehicles which

moved in or out of the parking spaces near the facility, and no delivery trucks or idling equipment was evident. During the noon period about ten vehicles and a tractor moved into and out of the adjacent University maintenance facility. During the sampling periods there was never a smell of exhaust gases as observed during the sampling in December. On June 17th there was even less movement of vehicles in front of the facility's air intake ducts. [Gay et al., 1987].

Although conversations with chamber operators indicate that they were vigilant in driving away idling delivery or maintenance vehicles when odors or chamber NOx monitors indicated the presence of tailpipe exhaust emissions in the chamber atmospheres, chamber VOC levels were not routinely monitored so a comparable continuous indicator of, for example, hot-soak gasoline vapor emissions from recently parked vehicles near the chamber inlet port was not available.

At CASAC's urging [USEPA, 1995a,b], Agency health researchers have addressed the potential for chamber artifacts briefly in a December 30, 1996 docket [ECAO-CD-92-0746] response:

Questions about non-ozone pollutants in chamber exposures was previously brought up in the CASAC Review Draft (see Response to Public and CASAC Review Comments on CH. 1)*. No specific contaminants of any toxicological significance have been measured or described in the peer-reviewed, published literature. In fact, the "paper trail" is questionable. The only known paper that discusses artifactual carbonyls resulting from ozonation of ambient air is by EPA authors (Tilton et al.) that was published as part of a measurement symposium (considered "grey" literature). It was approached as a QA issue by EPA. The hydrocarbon and carbonyl measurements in the EPA CLEANS facility in Chapel Hill, NC were spread over a 9-year period and were not part of a well-conceived research study. Although carbonyl measurements were reported, there was no attempt to "speciate" them, making any possible toxicological evaluation highly speculative. Even if aldehydes are the predominant carbonyl in the chambers, there are no available toxicological studies on the possible interaction between aldehydes and ozone, particularly at the low concentrations measured. (See attached documents [USEPA, (1995c)] for a full discussion of this issue.)

*[Chapter 1 comment] - Under guidelines established for production of the CD, only published, peer-reviewed papers are cited for discussion. No such contaminants of any toxicological significance have been measured or described in the literature.

Since the criteria document already includes such "grey" literature citations to AWMA specialty conferences, this EPA reason to ignore the chamber artifact issue is less than persuasive. Agency health scientists rather appear to question the methods ("not a well-conceived research study") and motives ("It is our view that it is basically, quite simply, a non-issue, it is essentially a red herring" - [USEPA, 1995a, p.74]) of the messengers [USEPA, 1995c]. The chamber atmosphere artifact peculiar to the EPA facility, DEAE, is not discussed in these recent EPA responses.

Although Tilton et al., 1994 report only the total carbonyl loadings, earlier EPA staff chamber

surveys [Bufalini et al., 1986; Gay et al., 1987] do speciate carbonyl compounds reporting a number of unknown "x"-aldehydes, comprising up to a third of the total carbonyl loading, that could not be identified through use of available standards. Also supporting the presence of non-ozone irritants are results from the 8-hour EPA chamber study conducted by Hazucha et al., 1992, where symptoms of eye irritation are reported. Twenty percent (4/20) of their subjects note a mild eye irritation during the ramped exposure tests when ozone levels are maximized. EPA [USEPA, 1995c] describes this symptom as characteristic of aldehyde exposure and not attributable to ozone.

Given the predominant role that EPA exposure chamber research plays in risk assessments conducted for the current ozone rulemaking, the Agency should promptly address the long-standing chamber artifact issue and determine the impact of these potential chamber irritants on reported responses to ozone exposure. The larger responses reported from the EPA facility should probably be considered suspect until this issue is resolved. Consequently, risks calculated from these results are likely excessive and provide an underestimate of the levels of protection provided by the existing standards.

o Chamber Dosing Profiles

There are other reasons to suspect that EPA may have overestimated exposure risks, such as the artificial dosing profiles used in the 6.6-hour chamber studies. During such studies subjects were exposed to constant O₃ concentrations for 6.6 hours at constant (40 L/min) breathing rates for 50 minutes of each hour with at-rest breathing during the final 10 minutes. A 30 minute lunch break in the chamber is included between the 3rd and 4th hours. Prolonged quasi-continuous ventilation at 40 L/min for 6-8 hours is unlikely to represent a lay understanding of "moderate" exercise, as it is characterized in the proposal. EPA health research scientists indicate that:

The exercise regimen of six 50-minute bouts of moderate exercise was intended to simulate work performed during a day of heavy to severe manual labor [Folinsbee et al., 1988] by outdoor laborers [McDonnell et al., 1991].

The criteria document agrees, noting [CD, 7-76] that "the 'moderate' exercise descriptor is based on previously published EPA guidelines for representative types of exercise (see Table 10.3, [USEPA, 1986]). Note, however, that exercise continued at this level (40 L/min) for 6 to 8 h should be considered as 'heavy' or 'strenuous work or play.'"

The EPA 6.6-hour exposure patterns are also unrealistic on several other counts. Constant ozone levels do not simulate ambient ozone levels that vary diurnally, typically peaking in the mid-afternoon with lower concentrations during the mornings and evenings. The Hazucha et al., 1992 study mentioned earlier also exposed subjects to an 8-hour triangular O₃ concentration pattern ranging from 0 ppm to 0.24 ppm at mid-exposure to 0 ppm and averaging 0.12 ppm over the 8-hour exposure period. Although the group mean FEV decrement (10.2%) peaked at 6 hours, group response had recovered to 6% after 8 hours, about the same value (5%) reported for this group after 8 hours at a constant 0.12 ppm exposure. These findings are supported by recent

Adams et al., 1997 results presented in Table 4. Group mean FEV decrements and $\Delta\text{FEV} \geq 15$ & 20% response rates in the Adams study generally increase from Exposure Pattern #1 to #2 to #3 as the normalized triangular O₃ concentration pattern becomes more acute. These studies suggest that dose-rate (or O₃ concentration) is more important than total dose and that functional decrements promptly adapt to changing exposures.

Nor do the constant breathing rates used in the 6.6-hour studies mimic natural variations during exercise. Recent studies monitoring breathing rates in children, outdoor workers, and outdoor construction workers [Spier, et al., 1991; Shamoo et al., 1991; Linn et al., 1993] indicate highly variable patterns of ventilation. In their recent study, Adams et al., 1997 simulate the variable breathing rate pattern developed by Johnson et al., 1997 for the maximally exposed construction worker (CW) monitored by Linn et al., 1993 in subjects exposed to constant 0.12 ppm O₃ levels over 6.6 hours (Table 4). Although the simulated mean CW breathing rates and O₃ dose in Exposure Pattern #4 averaged only 9% larger than the mean ventilation rates in Exposure Pattern #1, the group mean CW FEV decrement and response rates for FEV decrements ≥ 15 & 20% for Pattern #4 were 30-50% larger. Since O₃ concentration was held constant for these two treatments, the results suggest that dose rate, and not only O₃ concentration, is the important response variable for 6.6-hour exposures. Chamber response rates (e.g., the fraction of subjects with FEV decrements $\geq 15\%$) reported for constant O₃ and constant EVR exposures might be increased by up to 50% if acutely peaked diurnal O₃ patterns and variable ventilation rates with the same 6.6-hour average values were used instead. Studies of human ozone response should attempt to simulate both variations in O₃ concentrations and ventilation rates in order to provide the most realistic response data for use in risk assessments.

Finally, to the extent the EPA 6.6-hour studies were meant to simulate a day of "heavy to severe manual labor" [Folinsbee et al., 1988] by outdoor workers, the group mean exercise level chosen (40 L/min) appears to exceed measured group mean ventilation rates observed during workshifts (typically 8 hours but ranging from 6.6 to 11.6 hours) of outdoor construction workers. Linn et al., 1993 conducted continuous workshift ventilation measurements on 19 Los Angeles construction workers (carpenters, ironworkers, laborers), selecting individuals in this group with the most strenuous jobs. Individual workers within this group were closely supervised (and continuously observed by researchers) and vulnerable to early layoff if they did not appear to work hard. As a consequence, observed individuals within this group may have been especially "motivated" to maintain prolonged, elevated exercise levels. The group mean ventilation rate averaged 30 L/min during the workshift for these selected individuals in the most strenuous jobs. Since construction worker exercise involves the upper body to a greater-than-usual extent, arm-work effects on heart rate also likely lead to overestimates of ventilation for this cohort [Adams et al., 1996]. Although the EPA 6.6-hour protocol level may be realistic for the hardest-working "motivated" individuals (only 3 or 4 of the 19 Linn et al. workers were close to the EPA 40 L/min value), it overestimates the ventilation rate of a typical construction worker. Population risks estimated for such prolonged exercise patterns should probably be reduced several-fold to account for the modest fraction of individuals even within the selected high-exercise portion of such groups who will maintain such strenuous, multi-hour working patterns.

o Use of Adult Responses to Determine Children's Risks

In quantifying the children's risks tabulated in the proposal, the Agency acknowledges that

...acute exposure-response relationships developed were based on the clinical studies and were applied to "outdoor children" and "outdoor workers," and the general population. While these specific clinical studies only included adults aged 18-35, findings from other clinical studies and summer camp field studies in at least six different locations in the northeast United States, Canada and Southern California indicate changes in the lung function in healthy children similar to those observed in healthy adults exposed to O₃ under controlled conditions [61 FR 65724].

Whitfield et al., 1996 identify the relevant clinical and summer camp comparisons to be McDonnell et al., 1985 and Kinney et al., 1996 in their discussion of this assumption [p. 22]. A closer reading of these sources indicates that the similarity of responses between children and adults is less than supposed. Examined quantitatively, children's responses appear to be about half of those reported for adults. As a consequence, risks tabulated for children in the proposal may be overestimated by a factor of two from this assumption alone.

McDonnell et al., 1985 compare 8-11 year old male children to 18-30 year old male adults {McDonnell et al., 1983} exposed for 2.5 hrs to 0.12 ppm O₃ with intermittent exercise (alternating 15 minute periods of exercise and rest) at an EVR of 35 L/min/m² BSA:

The results of this study indicate that exposure of children to 0.12 ppm O₃ results in small decrements in FEV₁...similar to that reported by other authors [McDonnell et al. 1985]. ... The [clean] air group had decrements in [FEV₁ of 1%] and the 0.12 ppm group had significantly greater decrements of [5%]. These decrements are comparable to the ones reported here [for children] of [1%] for [clean] air and [3%] for ozone.

Group mean FEV decrements average 4% for adults and 2% for children, corrected for clean air exposure responses. Although "similar", children's responses are only about half those of adults in this comparison.

Kinney et al., 1996 reassess a collection of six summer camp studies comparing group mean slopes of FEV change with ozone exposure estimated from centrally located camp O₃ monitors. Study-specific FEV decrement slopes range from -0.19 to -1.26 ml/ppb O₃ over the six studies, about a seven-fold spread of ozone sensitivities suggesting confounding by other pollutants (e.g., ambient aeroallergen concentrations) or variables (e.g., average exercise levels). A combined slope for all six studies averaged -0.50 ml/ppb O₃, or about a 2.7% FEV decrement at 0.12 ppm O₃ exposure at the 2230 ml mean FEV for these summer camp children. However, the combined slope is halved, to -0.26 ml/ppb O₃, when corrected for training effects (time variant trends in FEV measurement) that occurred over the multi-week camp attendance periods, a fact that EPA fails to consider in their characterization of these studies [USEPA, 1996c, p. 32]. Rather, the Agency uses the "similarity" of responses in the summer camp responses and in the

single 2.5-hour chamber study of heavily exercising children [McDonnell et al., 1985] to chamber studies of adult responses as the basis of their rationale for ascribing adult dose-response functions to children in risk assessments used to propose revised standards. The corrected mean FEV decrement in the summer camp studies is thus about 1.4% averaged across studies, about a third of the 4% response reported above for adults in McDonnell et al. 1985.

McDonnell et al., 1995 note a strong age-related decline in adult FEV decrements $\geq 10\%$ during 6.6-hr exposures to 0.12 ppm O₃: 67% of 20-year old subjects achieve this response compared to 46% of 25-year olds and 28% of 30-year olds. On the basis of the above comparisons children (< 18 years old) and older adults (> 25 years old) may also be less responsive than the 18-25 year old young adults that dominate the EPA 6.6-hour study cohorts. The failure of the EPA risk assessment to account for such age-related differences in population responses should lead to substantial underestimates of the level of protection afforded by current standards.

o Neglect of EVR Effects in Calculation of 6.6-Hour Headcount Risks

In computing 8-hour risks, Whitfield et al., 1996 are limited to constructing dose-response functions from EPA studies measuring responses to O₃ levels of 0.00, 0.08, 0.10 and 0.12 ppm at a single breathing rate, nominally 40 L/minute. However, since subjects participating in these studies were of different sizes, their equivalent ventilation rates (EVR) spanned a two standard deviation range of ± 7 L/min/m² about a mean EVR of 20 L/min/m². Accordingly, as discussed in Whitfield et al., 1996 [pp. 36-37], the products of the derived dose-response functions and pNEM/O₃-generated exposure distributions of individuals with EVRs ranging between 13 and 27 L/min/m² were summed over O₃ concentration levels to generate the EPA risk estimates. However, this approach assumes that O₃ responses measured at 20 EVR are the same as those at 13 and 27 EVR. If both the dose-response curve and the distribution of exposures vary with EVR, this approximation grossly overestimates projected risks.

It is reasonable to expect that 8-hour responses at a given concentration will vary with EVR since 1- and 2-hour exposure-response studies show a strong variation [CD, 9-16]. In Figure 9-1 of the criteria document group mean FEV decrements from intermittent 2-hour, 0.5 ppm O₃ exposures increase from 8% to 13% to 16% to 28% at EVRs of < 12, 13-22, 23-32, and > 34. Individual FEV decrements for the 31 Folinsbee/Horstman subjects exposed to 0.12 ppm can be grouped by individual EVR as tabulated below in Table 5a. The resulting estimated responses suggest that 6.6-hour Δ FEV $\geq 15\%$ response rates will be lower at 13 EVR and higher at 27 EVR than the 38% response rate projected for 20 EVR at 0.12 ppm by Whitfield et al. [Figure B.28, p. 113].

Table 5a - EVR Dependence of Folinsbee/Horstman 6.6-hr FEV $\geq 15\%$ Responses to 0.12 ppm

No. of Subjects	EVR Median	EVR Range	mean Δ FEV (SD) (%)	Response Rate Δ FEV $\geq 15\%$ (%)
9	17	16.1-19	10.4 (11.1)	3/9 (33%)
13	20	19.1-22	12.3 (12.3)	5/13 (38%)
9	23	22.1-24	13.5 (13.5)	7/9 (77%)

Table 5b presents estimated dose-response curves by EVR category, assuming zero responses at 0.04 ppm and FEV decrement $\geq 15\%$ response rates from 6.6-hour exposures at 0.12 ppm O₃ from Table 5a. For the purpose of sensitivity testing, $\Delta\text{FEV} \geq 15\%$ responses rates were

Table 5b - Estimated EVR Dependence of $\Delta\text{FEV} \geq 15\%$ Response Rates Corrected for 0.04 ppm Background Response Rates

O ₃ median	O ₃ range/EVR	13	17	20	23	27	20W
51 ppb	41-60 ppb	.0138	.0454	.0523	.1059	.1375	.0412
66	61-70	.0325	.1073	.1235	.2502	.3250	.1147
76	71-80	.045	.1485	.1710	.3465	.4500	.1637
86	81-90	.0575	.1898	.2185	.4428	.5750	.2127

assumed to be 10% and 100% at 13 EVR and 27 EVR, respectively. In the manner of Whitfield et al., 1996 [pp. 29-35] two-point EVR-specific dose-response curves were fit to the 0.04 and 0.12 ppm data to compute the intermediate values presented in Table 5b. The Whitfield dose-response curve (20W), included in Table 5a for comparison, is very similar to the 20 EVR dose-response function derived from Table 5a. If the response functions in Table 5b are corrected for 0.06 ppm background responses, Table 5c is the result. An example of the EVR dependence of

Table 5c - Estimated EVR Dependence of $\Delta\text{FEV} \geq 15\%$ Response Rates Corrected for 0.06 ppm Background Response Rates

O ₃ median	O ₃ range/EVR	13	17	20	23	27	20W
66	61-70	.0075	.0250	.0288	.0583	.0750	.0294
76	71-80	.0200	.0667	.0769	.1556	.2000	.0784
86	81-90	.0325	.1083	.1250	.2528	.3250	.1273

exposures estimated by the pNEM/O₃ model is provided below in Table 6 for Los Angeles outdoor workers subject to 1991 "as is" air quality. The table includes 97% of the total occurrences (107 million person-days) of daily maximum 8-hour exposures for this cohort by concentration and EVR interval. The remaining 3% are principally in the < 15 EVR column at higher O₃ concentrations. The table illustrates the strongly peaked nature of the pNEM/O₃ exposure distributions at low EVR levels. Occurrence rates change by orders of magnitude for

Table 6 - Percent of LA Outdoor Worker 8-hour Daily Maximum Occurrences by EVR Interval

O ₃ /EVR	<15	15-24	25-29	30-34	35+
<40 ppb	68	0.5	0.04	0.0003	0
41-60	19.5	0.1	0.006	0.000004	0
61-70	4.2	0.02	0.002	0.0002	0
71-80	2.8	0.01	0	0	0
81-90	1.7	0.004	0.001	0.0007	0

each EVR interval within a given concentration range. Accordingly, Whitfield's current calculations of O3 risk will be driven by the responses of the low EVR portions of the exposure distributions whose actual responses are likely much less than those measured for subjects at 20 EVR. Overestimation of population risks are likely to result from this Whitfield et al., 1996 approximation.

For illustrative purposes, a crude estimate of this error might be derived by comparing risks calculated from Tables 5a, 5b and 6 as described by Whitfield et al., 1996 [pp.36-37]. Using their approach and data from Table 5a, all exposures above 0.04 ppm presented in Table 6 are evaluated using a single dose-response function (20W) with a calculated result of 0.02115. Thus about 2% of the 1991 LA outdoor worker 8-hour daily maximum exposures are projected to result in FEV decrements $\geq 15\%$; this amounts to about 8 per outdoor worker per year in a year with annual highest daily maximum 1- and 8-hour O3 values of 0.32 ppm and 0.22 ppm, respectively [Johnson, 1995]. Applying the EVR-specific dose-response functions for 13, 20 and 27 EVR to the < 15, 15-24, and 25-29 EVR categories in Table 6 yields a result of 0.00642, about a third of the value calculated with the 20W dose-response function that neglects the effects of EVR on response. If EVR < 15 is actually below the $\Delta\text{FEV} \geq 15\%$ response threshold for 8-hour exposures, the calculated value would be 0.000123 and risks would be overestimated 170-fold.

A similar exercise assuming a 0.06 ppm background and using data in Table 5c yields 20W results of 0.005615, a value only a quarter as large as that calculated for 0.04 ppm background levels. The corresponding EVR-specific calculation yields a result of 0.00145, a value a quarter again lower than the 20W approach. Thus the 2.1% response rate calculated for this cohort by the Whitfield approach would fall to 0.15% if calculated for an 0.06 ppm O3 background and EVR-sensitive dose-response functions, a 15-fold reduction in risk.

o Estimated Conservatism of Calculated Ozone FEV Decrement $\geq 15\%$ Risks

It is interesting to speculate on the degree that projected risks tabulated in the proposal for children might be overestimated by assumptions discussed above for the exposure and risk models used by the Agency. Table 7 collects a number of these assumptions, cites sources of information, and provides estimated adjustment factors. If these factors are reasonably independent, then the product of these factors will yield an order of magnitude estimate of modeled risk conservatism. The simple product of these factors equals 0.0076, indicating about a 100-fold overestimate of $\Delta\text{FEV} \geq 15\%$ risk⁴ in outdoor workers and likely also in children.

⁴ Risk as defined by EPA.

Table 7 - Estimated Adjustments to EPA 6.6-hour Chamber Data and ORAMUS Risk Model Used to Calculate Children's 8-hour FEV Decrement \geq 15% Risks

Adjusted Exposure/Risk Assumption Factor	Data/Analysis Source	Adjustment
1. Ambient O3 Monitoring Error	Johnson et al., 1996a	0.6
2. Motivated Exerciser	Johnson, 1996; Table 2	0.75
3. Compositing Parameters	Johnson, 1996; Table 2	0.41
4. Elasticity Adjustment	Johnson, 1996; Table 3	1.3
5. 0.06 ppm bkg O3 Exposure Adjustment	Whitfield & Richmond, 1996	0.75
6. 0.06 ppm bkg O3 d-r Adjustment	Whitfield et al., 1996 (Fig B.28)	0.8
7. Attenuation Adjustment	Folinsbee et al., 1994	0.85
8. EPA Chamber Artifacts	Adams et al., 1997; Table 4	0.5
9. Use of Constant O3 & EVR Exposures	Adams et al., 1997; Table 4	1.5
10. Use of 40 L/min Ventilation	Linn et al., 1993 & 1994	0.5
11. Use of Adult d/r for Children	McDonnell et al., 1985 & Kinney et al., 1996	0.5
12. EVR-Invariate d-r Adjustment	Whitfield et al., 1996 Folinsbee et al., 1988 Horstmann et al., 1990	0.33

o Hospital Admissions Risks

Compared to uncertainties in risks assessed from chamber or summer camp studies, those in analyses based on epidemiological estimates of dose-response are greatly expanded. Such approaches are confounded by meteorological variables, aeroallergens, other potentially confounding pollutants, and poorly known personal exposures. The Administrator appears to recognize a number of these difficulties [61 FR 65726]. As noted, even with the lesser reliability of such studies, the proposed standard would reduce projected NYC total asthmatic O3-related admissions risks by only 0.6%.

This small benefit would be reduced further if 0.06 ppm rather than 0.04 ppm O3 background risks were taken into account. Thurston et al., 1992 project median asthmatic hospital admission rates of 0.5, 0.7 and 1.4 per million people for daily maximum hourly ozone levels of 0.04, 0.06, and 0.12 ppm. When corrected for background effects at 0.04 ppm, the admissions rate at 0.12 ppm drops to 0.9 per million people. Correction of the dose-response function for 0.06 ppm background effects would lower the 0.12 ppm admissions rate by half, to 0.7 per million. After accounting for reduced exposures in the 0.04-0.06 ppm interval and background adjustments in the dose-response function in a corrected risk assessment, the proposed standard would probably reduce projected total O3-related asthmatic NYC admissions by less than 0.5% per year. Whitfield et al., 1996 may also have inflated NYC admissions risk by applying epidemiological response estimates derived for the peak pollutant period (June-August) to the entire 214 day

smog season.

Conclusions

In summary, the preceding analysis identifies a number of reasons to suspect that the levels of protection afforded by the current standards are much larger than currently assumed by the Agency. Taken together, these reasons suggest that the quantitative risk assessment used in the proposal likely overestimates O3 FEV decrement risks to children by over an order of magnitude. As noted in Table 8, risks projected for the next most susceptible group, identified

Table 8 - Percent of Outdoor Workers Estimated to Experience Various Health Effects 1 or More Times per Year Associated with 8- and 1-Hour Ozone Exposures Upon Attaining Alternative Standards*

Level	Standard Form	Abbreviation	8-hr ΔFEV ≥ 15%	8-hr ΔFEV ≥ 20%	1-hr PDI
0.07ppm	8-hr, 1 ExEx	07/8HR/1EX	0.8 (0.2-1.9)**	0.03 (0.01-0.4)	0.15 (.00-1.3)
0.08	8-hr, 1 ExEx	08/8HR/1EX	1.4 (0.5-3.2)	0.17 (0.06-0.8)	0.27 (.01-1.7)
0.09	8-hr, 1 ExEx	09/8HR/1EX	1.9 (0.7-4.3)	0.25 (0.08-1.1)	0.50 (.04-2.5)
0.12	1-hr, 1 ExEx	12/1HR/1EX	2.1 (0.7-4.7)	0.28 (0.09-1.2)	0.55 (.05-2.6)

* Acronyms: ΔFEV = forced expiratory volume decrement in one second; PDI = moderate to severe pain upon deep inspiration; ExEx = annual expected exceedances; 8107 = 8-h, 1 ExEx, 0.07 ppm standard. Estimates aggregated over 9 urban areas
 ** 90% credible interval

by EPA, outdoor workers, for FEV decrements ≥ 15% & 20% and PDI would be lower by factors of 4, 10 and 2 than those projected for outdoor children [API, 1996]. The risks to the general population would be lower still since this cohort spends less time outdoors and at elevated exercise levels. Given the newly realized margins of safety encompassed in current regulations, the perceived pressure to regulate now is lessened and the Agency has an opportunity to conduct research needed to resolve lingering uncertainties to ensure that the benefits of revision are worth the burdens of implementation.

Considering the impacts of revision, EPA should reconsider its action and reaffirm the current primary standard. Should EPA feel compelled to issue a revised standard for non-health reasons, it should be no more stringent than the current standard and of a form that would minimize the implementation burden. This course would bring it into agreement with the conclusions of the Clean Air Scientific Advisory Committee impaneled to evaluate the technical bases of revision who found that none of the alternative standards under consideration were significantly more protective of the public health. The Agency would also be supported in its reconsideration by the conservatism of existing EPA monitoring and modeling policies as well as recent evidence indicating that levels of protection provided by the current and alternative standards are larger than previously assumed.

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