



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Office of Air Quality Planning and Standards
Research Triangle Park, North Carolina 27711

November 4, 1993

MEMORANDUM

SUBJECT: Los Angeles Ozone Exposure Estimates

FROM: Tom McCurdy *Tom*
Ambient Standards Branch (MD-12)

TO: Interested Parties

SUMMARY

This memo summarizes analyses that I have done on ozone (O_3) exposure estimates for Los Angeles produced by International Technology - Air Quality Services (IT-AQS). The estimates are a result of applying our pNEM/ O_3 exposure model to six air quality scenarios representing 1991 "as is" conditions and five hypothetical situations when alternative 1h and 8h O_3 standards are just attained. Unless otherwise noted, the exposure estimates provided in this summary represent the mean value of ten runs of the model.

The analyses were undertaken for the total population--excluding outdoor workers--and for children. Outdoor worker exposures will be evaluated in the next few months when a better human activity data base can be constructed for outdoor workers than we currently have.

Analyses of "as is" air quality conditions for the year 1991 indicate that:

- 1) 80% of the total non-outdoor working population at "any" breathing rate experiences one or more exposures >0.12 ppm on a 1h daily maximum basis.
- 2) While at a high exercise level (equivalent ventilation rate (EVR) of 30 or higher), only 9% of the total non-outdoor working population experiences one or more exposure >0.12 ppm (1h maximum daily basis). For children only, the percentage who experiences one or more exposures >0.12 ppm (1h maximum daily basis) at this exercise level is 27%.

- 3) 11% of the total non-outdoor working population experiences one or more exposures >0.08 ppm 8h daily maximum average when at a breathing rate of 15 EVR or higher; 37% percent of the children experiences such an exposure at the same breathing rate.
- 4) 21% percent of the total non-outdoor working population experiences one or more exposure >0.06 ppm 8h daily maximum average when at a breathing rate of 15 EVR or higher; 69% of the children experiences such an exposure at the same breathing rate.

The analyses of 5 alternative standards (1h 1 Ex 0.12 ppm; 8h 1 Ex 0.10 ppm; 8h 5 Ex 0.08 ppm; 8h 1 Ex 0.08 ppm; and 8h 5 Ex 0.06 ppm) indicate that when any alternative standard that was examined is just attained, the percentage of the exposed population is sharply reduced. For all cases, except the 8h 1 Ex 0.10 alternative, the percentage of both the total non-outdoor work population and children alone exposed at exercise one or more times to the level of concern is well below 1%. The 8h exposures to 0.08 ppm or higher for the 8h 1 Ex 0.10 alternative are 1% for the total non-outdoor working population and 3% for children. These analyses also found that for all air quality scenarios that were examined, just attaining an alternative O₃ standard reduces multiple-day exposures for the air quality/exercise levels of interest.

DETAILS

IT-AQS has completed its modeling of O₃ exposures estimates for six air quality scenarios. Those scenarios are:

1. 1991 air quality--the "as is" scenario
2. Attain 1h 1Ex 0.12 ppm--the current standard
3. Attain 8h 1Ex 0.08 ppm
4. Attain 8h 1Ex 0.10 ppm
5. Attain 8h 5Ex 0.06 ppm
6. Attain 8h 5Ex 0.08 ppm

The model used for exposure assessment is the most recent version of pNEM/O₃--"probabilistic" NAAQS Exposure Model applied to O₃. The model is described in a draft IT-AQS report entitled:

Estimation of Ozone Exposures Experienced by Urban Residents Using a Probabilistic Version of NEM and 1990 Population Data (September 1993).

The report was written by Ted Johnson, project manager for IT-AQS, and two of his staff members: Jim Capel and Mike McCoy.

Modeling results exist for all nine urban areas that we plan to evaluate. We wanted to model a year that allowed us to reasonably match up 1990 census data with air quality information. We used 1990 or 1991 as the year of analysis in an area, using the year with the greatest number of O₃ monitors reporting valid data. The following situations were modeled:

<u>Urban Area</u>	<u>Year</u>	<u>Population</u>
Chicago	1991	6,175,000
Denver	1990	1,485,000
Houston	1990	2,371,000
Los Angeles	1991	10,371,000
Miami	1991	1,942,000
New York	1991	10,658,000
Philadelphia	1991	3,786,000
St. Louis	1990	1,707,000
Washington, DC	1991	3,085,000

All of these areas violated the existing O₃ standard in the year analyzed except Miami. The areas are located in every EPA region, except 10--the northwest, which has only one non-attainment area (Portland).

While modeling results exist for the above areas, they have not yet been analyzed or summarized. Only the Los Angeles results have been thoroughly evaluated, and these results are described in this memo.

Estimates for two population groups will be described: (1) all people except outdoor workers--who constitute about 10% of the adult working population, and (2) children--everyone younger than 19 years of age. Outdoor worker exposure estimates will be evaluated after IT-AQS can construct a larger file of human activity patterns that better reflect the amount of time that true outdoor workers (i.e., those individuals who work outdoors at least 6 hours per day, on average) spend outside in their daily occupation. In developing this new data base, we will probably focus on people working in the following industrial classification categories:

1. agriculture, forestry and fisheries (101-031)
2. mining (040-050)
3. construction (060)

These workers currently are under-represented in our NEM human activity data base.

Our results are based upon 10 runs (realizations) of pNEM/O₃ for each air quality scenario. Based on my previous analyses of sets of 10-run results versus a 108-run result (see the attached April 19, 1993 memo), I feel that the estimates presented here

adequately represent the mean and overall distribution expected if more runs of pNEM/O₃ were undertaken. What 10-runs do not adequately represent, however, is the entire range of possible outcomes. More runs could only increase this range.

This memo includes tabular and graphical data on (1) the number and percent of people exposed, and (2) the number and percent of person-occurrences for the two population groups mentioned above. Even though data are discussed here regarding the absolute and relative (percentage) number of people exposed, it must be remembered that we really should not be using "people" as an exposure metric. The cohort-specific activity-days data base used for pNEM/O₃ modeling (and for all other exposure models that uses human activity information) is based upon one, two, or three days of data from a single individual. Thus, inferences from these data rigorously can only be made to "person-days" of exposure, or "person-occurrences" of exposure, where an occurrence can be 1h, 8h, or a day in pNEM/O₃. This metric also applies to children-occurrences or children-days of exposure.

Only if activity data are available sequentially for an entire year for individuals in a cohort can inferences be made to people (or kids, or outdoor workers as the case may be). This point is never discussed in the general exposure assessment literature but should be.

Data for three exposure indicators are included.

1. daily maximum dose 1h exposures >.12 ppm at an equivalent breathing rate (EVR) of 30 liters or higher per minute per square meter of body surface area ($1 \text{ min}^{-1} \text{ m}^{-2}$). This is about 55-60 1 min^{-1} for adults. These results are shown in Table 1 and Figure 1.
2. daily maximum dose 8h exposures >0.08 ppm at 15 EVR. This is about 20-30 1 min^{-1} for adults and 12-25 1 min^{-1} for children. These results are depicted in Table 2 and Figure 2.
3. daily maximum dose 8h exposures >0.06 ppm at 15 EVR. See Table 3 and Figure 3 for results.

Other indicators were evaluated and many others can be evaluated. One of the purposes of this memo is to obtain definitive feedback on what indicators should be presented in the O₃ staff paper. Therefore, please review the information presented to see if all exposure indicators of interest and importance are covered.

As an example of an available but unreported indicator, daily max dose 8h exposures to 0.10 ppm or higher were analyzed. However, exposures at this high an 8h average were seen only under the "as is" air quality scenario. Hence, I do not provide

a table/figure for this indicator. For the record, however, pNEM/O₃ indicates that currently 630,700 people on average are exposed to 8h 0.10 ppm or higher for an average of 1.4 times per year. This is about 6.1% of the LA population that was analyzed. The range in population estimate is 527,100-814,700, or 5.1-7.9%. The range in occurrences per exposed person is 1.3-1.7 times per year.

To put the numbers and percentages that follow into perspective, the baseline "denominators" used in the Los Angeles analyses are:

Total population : 10,371,115
Children population : 1,954,886

Total daily maximum person-occurrences: 3,785,456,975
Total daily children-occurrences: 713,533,390

Total hourly person-occurrences: 90,850,867,400

Exposures to the air quality levels of interest are much higher, of course, at "any" breathing rate than at the relatively high breathing rates of interest. The following statistics are for exposures to 1h and 8h concentrations of interest at any breathing rate for the "as is" air quality scenario:

	1h 0.12 ppm	8h 0.10 ppm	8h 0.08 ppm	8h 0.06 ppm
Mean Number of People Exposed	8,305,200	4,556,100	7,196,600	9,872,400
Mean % of Tot. Population	80.1	43.9	69.4	95.2
Range in this Percentage	76.7-82.7	40.8-51.2	67.3-71.2	94.1-97.2

Note the relatively high mean percentage estimates and the quite narrow range in these estimates. The 1h 0.12 ppm estimate of 80.1% of the total population is about 15% lower than comparable estimates from previous REHEX and SAI/NEM O₃ modeling analyses. Their runs, however, are for the late 1980 time period when O₃ air quality was worse than it currently is (i.e. than 1991, our "as is" year).

In fact, two districts in the Los Angeles area did not exceed a 0.12 ppm 1h O₃ concentration level in 1991. These districts are Long Beach and Hawthorne. They comprise about 15% of the modeled urban area population base and include major employment centers that boost daytime inhabitants to over that relative level. Thus, the 80% estimate is plausible given the

amount of time spent indoors by most people, especially in air conditioned spaces where O_3 levels are a fraction (1/4 to 1/2) of that seen outside at the same time.

Other modeling differences can account for the disparity in people estimated to experience a 0.12 ppm O_3 level. For instance, the two non-EPA studies noted above used modeled O_3 air quality data, whereas ours used transformed ambient monitoring data. In addition, our pNEM/ O_3 analyses explicitly incorporates sequential time spent indoors as a function of time-of-day, whereas REHEX does not and SAI/NEM used the old 1982 NEM activity patterns that are out of date.

A more in-depth review of the outputs follows.

Table 1/Figure 1

pNEM/ O_3 estimates that 9.1% of the total population currently experiences O_3 exposures >0.12 ppm 1-h at high exercise (≥ 30 EVR). Over half (56%) of these people are children, and over 25% of children (27.1%) experience one or more of these exposures per O_3 season (i.e., per year in LA). About 42% of the exposed children experience more than 1 day of exposure at a 1h 30 EVR or higher.

Attaining any of the alternative ambient standards listed in Table 1 dramatically reduces 1h O_3 exposures at high exercise. Attaining the last two standards (the 8h 1Ex 0.08 and 8h 5EX 0.06 scenarios) reduces 1h high-exercise exposures to zero. Note that no child or person would be exposed to more than one day of 0.12 1h @30 EVR exposure if any alternative O_3 NAAQS analyzed here is attained.

Some of the data shown in Table 1 is depicted in Figure 1. The figure is good for depicting the range in estimates for any scenario. Note that the middle-three scenarios have 3-5 orders of magnitude of range in their estimates of 1h 0.12 ppm @30 EVR exposures. This is a much larger range than seen in previous NEM exposure analyses, and probably reflects the higher--and in my opinion, better--ventilation rate data recently developed by IT for the high exercise level.

Table 2/Figure 2

More people, both absolutely and relatively, are exposed to 0.08 ppm 8h @ 15 EVR than to 0.12 ppm 1h @ 30 EVR for all the air quality scenarios except the last one. The differences are larger for children than for the entire population. For instance, Table 2 indicates that almost 37% of children currently see 0.08 8h @15 EVR one or more times/year (range: 31-44%). About 51% of these exposed children see more than one exposure/year.

Table 1. ESTIMATES OF 1H OZONE EXPOSURES IN LOS ANGELES > 0.12 PPM @ 30 EVR^a ONE OR MORE TIMES PER OZONE SEASON UNDER SIX AIR QUALITY SCENARIOS

Statistic	Air Quality Scenarios					
	As Is Situation (1991)	Attain 8h 1Ex 0.10 ppm	Attain 8h 5Ex 0.08 ppm	Attain 1h 1Ex 0.12 ppm	Attain 8h 1Ex 0.08 ppm	Attain 8h 5Ex 0.06 ppm
TOTAL EXPOSED POPULATION						
Mean Estimate of the Number of People	947,400	23,100	3,000	900	0	0
Percent of Total Population	9.1	0.2	*	*	0	0
Range in This Percentage	7.2 - 11.4	0.0 - 0.7	0.0 - 0.2	0.0 - 0.1	-	-
Mean Est. of Person-Occurrences	1,097,500	23,100	3,000	900	0	0
Percent of Total Per.-Occurrences	0.03	@	@	@	0	0
Mean Est. of Occurrences/Person Exposed	1.2	1.0	1.0	1.0	0	0
Percent of People > 1 Day/Year Exposure	31.0	0	0	0	0	0
EXPOSED CHILDREN						
Percent of Total Exp. Pop. Who are Children	56.0	85.0	53.0	100.0	-	-
Mean Estimate of the Number of Children	530,400	19,700	1,600	900	0	0
Percent of Children	27.1	1.0	0.1	*	0	0
Range in this Percentage	18.8 - 31.8	0.0 - 3.4	0.0 - 0.8	0.0 - 0.5	-	-
Mean Est. of Children-Occurrences	949,200	19,700	1,600	900	0	0
Percent of Total Child.-Occurrences	0.1	@	@	@	0	0
Mean Est. of Occurrences/Child Exposed	1.8	1.0	1.0	1.0	0	0
Percent of Children > 1 Day/Year Exposure	42.0	0	0	0	0	0

Notes:

^aEquivalent ventilation rate. It is equal to ventilation rate ÷ body surface area; units are in $l \text{ min}^{-1} \text{ m}^{-2}$.

*Less than 0.05% but > 0.

@Less than 0.005% but > 0.

Figure 1. NUMBER OF PEOPLE IN LOS ANGELES WHO ARE EXPOSED ONE OR MORE TIMES PER YEAR TO 1H OZONE LEVELS 0.12+ PPM @ 30 EVR OR HIGHER

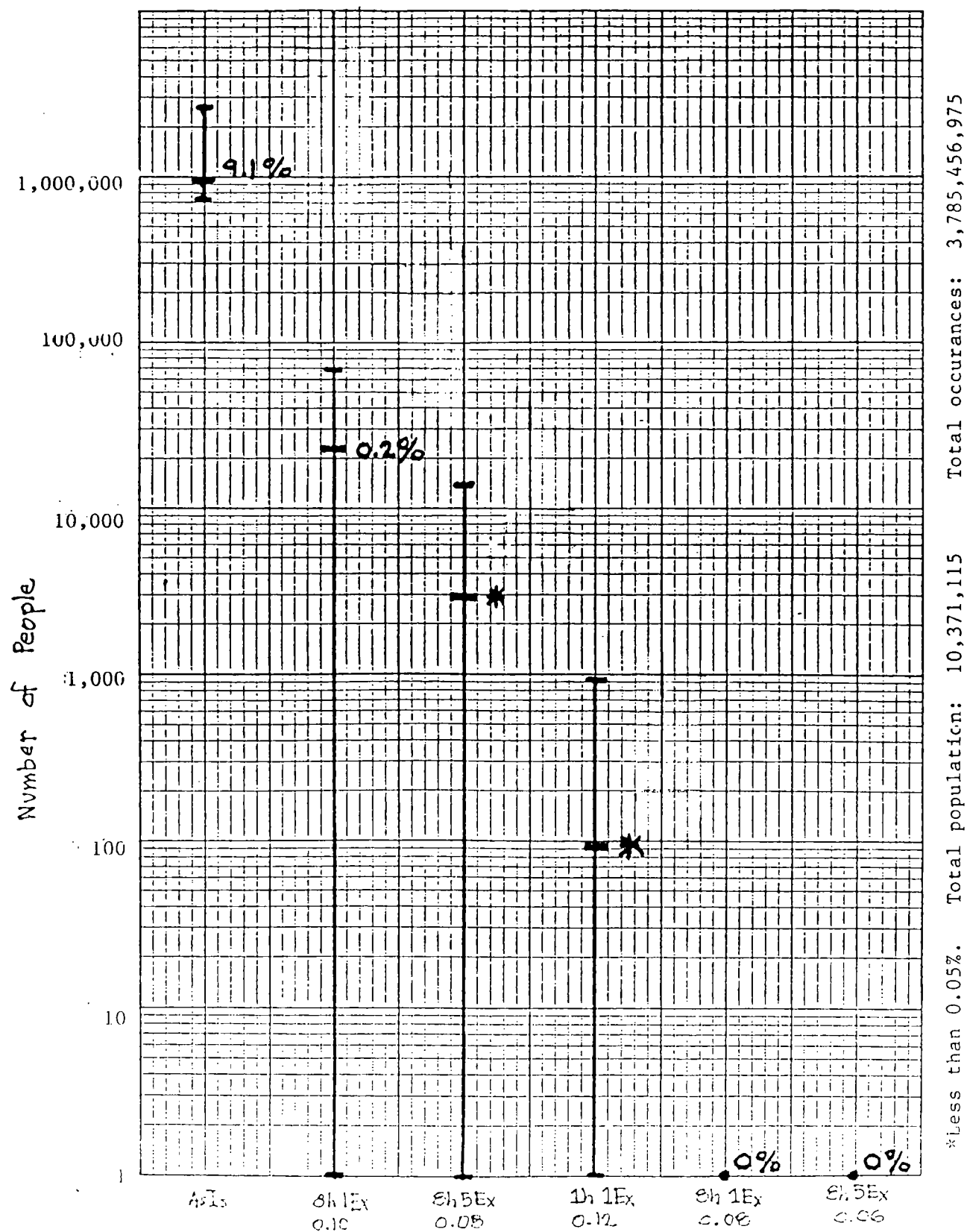


Table 2. ESTIMATES OF 8h OZONE EXPOSURES IN LOS ANGELES TO 0.08 PPM OR HIGHER @ 15 EVR^a ONE OR MORE TIMES PER OZONE SEASON UNDER SIX AIR QUALITY SCENARIOS

Statistic	Air Quality Scenarios					
	As Is Situation (1991)	Attain 8h 1Ex 0.10 ppm	Attain 8h 5Ex 0.08 ppm	Attain 1h 1Ex 0.12 ppm	Attain 8h 1Ex 0.08 ppm	Attain 8h 5Ex 0.06 ppm
TOTAL EXPOSED POPULATION						
Mean Estimate of the Number of People	1,122,800	106,300	7,700	5,000	1,700	0
Percent of Total Population	10.8	1.0	0.1	*	*	0
Range in This Percentage	9.3 - 13.5	0.6 - 1.7	0.0 - 0.2	0.0 - 0.1	0.0 - 0.1	-
Mean Est. of Person-Occurrences	1,990,300	116,200	7,700	5,000	1,700	0
Percent of Total Per.-Occurrences	0.05	@	@	@	@	0
Mean Est. of Occurrences/Person Exposed	1.8	1.1	1.0	1.0	1.0	0
Percent of People > 1 Day/Year Exposure	45.0	7.7	0	0	0	0
EXPOSED CHILDREN						
Percent of Total Exp. Pop. Who are Children	63.9	61.3	49.4	0	41.2	-
Mean Estimate of the Number of Children	718,000	65,200	3,800	0	700	0
Percent of Children	36.7	3.3	0.2	0	*	0
Range in this Percentage	30.8 - 43.5	0.5 - 7.6	0.0 - 0.7	-	0.0 - 0.4	-
Mean Est. of Children-Occurrences	1,389,300	72,500	3,800	0	700	0
Percent of Total Child.-Occurrences	0.2	*	*	0	*	0
Mean Est. of Occurrences/Child Exposed	1.9	1.1	1.0	0	1.0	0
Percent of Children > 1 Day/Year Exposure	51.3	N/A	0	0	0	0

Notes:

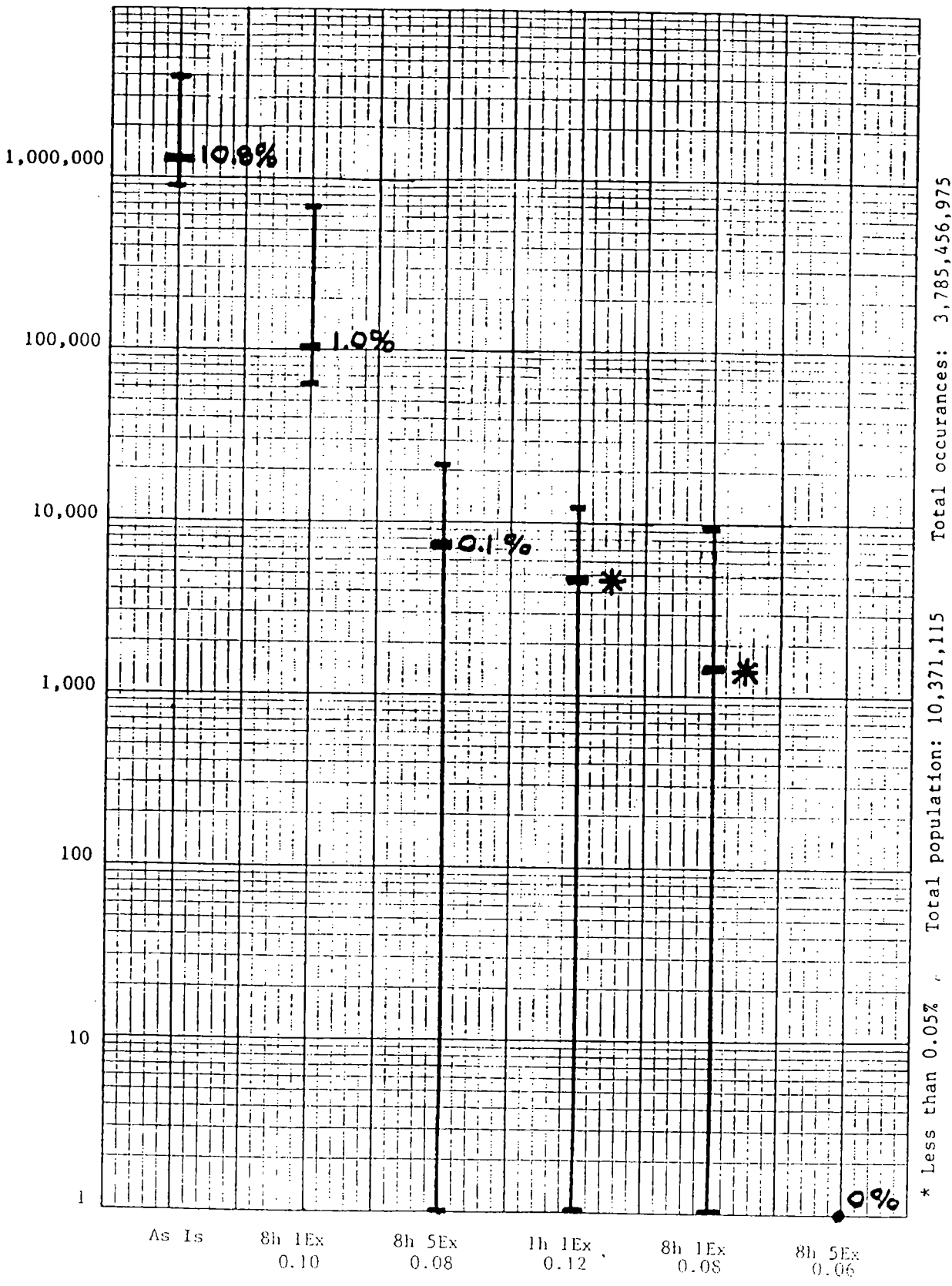
^aEquivalent ventilation rate. It is equal to ventilation rate ÷ body surface area; units are in l min⁻¹ m⁻².

*Less than 0.05% but > 0.

@Less than 0.005% but > 0.

N/A Not available.

Figure 2. NUMBER OF PEOPLE IN LOS ANGELES WHO ARE EXPOSED ONE OR MORE TIMES PER YEAR TO 8H OZONE 0.08+ PPM @ 15 EVR OR HIGHER



The estimates of exposure to 0.08 ppm 8h @15 EVR drop rather rapidly with attainment of the alternative NAAQS. See Figure 2. Note again the rather large range in estimates for the middle three scenarios.

Table 3/Figure 3

The air quality indicator of interest here is 0.06 ppm 8h @ 15 EVR. Because this is a relatively low 8h average for Los Angeles, a large number and percentage of people experience this exposure for all of the scenarios evaluated. Contrary to the previous indicators, except for the last NAAQS air quality scenario, the indicator range estimated for each scenario is quite narrow.

Most of the people exposed to 0.06 ppm 8h @ 15 EVR or above are children. The proportion of children only varies between 61-74% for the first 5 scenarios. (This jumps to 86% for the last, quite low 8h 5Ex 0.06 ppm scenario.)

Table 3 does not include an estimate of the percent of exposed children or the total population that sees more than one day/season over the indicator of interest. It just was too much work to evaluate that data for this preliminary analysis; the data are available to obtain that estimate, however. A superficial examination of this exposure indicator, however, indicates that all (100%) of children exposed to 0.06 ppm for 8h at 15+ EVR saw more than one day per year under the first two air quality scenarios. While this percentage drops off for the next 3 scenarios, some children and adults obviously saw more than 1 day per year (because mean occurrences/personal exposed is >1.0). No one saw more than 1 day for the 8h 5EX 0.06 ppm scenario, the alternative that allows up to five exceedances per year.

FINAL COMMENTS

The results presented here represent only a fraction of the data available from pNEM/O₃ modeling exercise. Comments and recommendations are hereby solicited regarding the type of exposure indicators evaluated, the format of presentation, and emphasis. All comments and questions regarding this memo and the pNEM/O₃ modeling effort should be directed to Tom McCurdy at the address given above or by calling (919)541-5658.

Table 3. ESTIMATE OF 8h OZONE EXPOSURES IN LOS ANGELES TO 0.06 PPM OR HIGHER @ 15 EVR^a ONE OR MORE TIMES PER OZONE SEASON UNDER SIX AIR QUALITY SCENARIOS

Statistic	Air Quality Scenarios					
	As Is Situation (1991)	Attain 8h 1Ex 0.10 ppm	Attain 8h 5Ex 0.08 ppm	Attain 1h 1Ex 0.12 ppm	Attain 8h 1Ex 0.08 ppm	Attain 8h 5Ex 0.06 ppm
TOTAL EXPOSED POPULATION						
Mean Estimate of the Number of People	2,193,600	554,000	170,200	246,000	198,700	6,300
Percent of Total Population	21.2	5.3	1.6	2.4	1.9	0.1
Range in This Percentage	19.9 - 22.9	4.4 - 6.2	0.9 - 3.1	1.5 - 3.7	1.2 - 3.1	0.0 - 0.3
Mean Est. of Person-Occurrences	4,797,200	798,400	202,600	292,300	231,700	6,300
Percent of Total Per.-Occurrences	0.11	0.02	@	0.01	@	@
Mean Est. of Occurrences/Person Exposed	2.2	1.4	1.2	1.2	1.2	1.0
EXPOSED CHILDREN						
Percent of Total Exp. Pop. Who are Children	61.1	68.8	73.7	64.3	68.5	85.7
Mean Estimate of the Number of Children	1,339,400	381,200	125,400	158,200	136,100	5,400
Percent of Children	68.5	19.5	6.4	8.1	7.0	0.3
Range in this Percentage	62.6 - 73.6	15.0 - 23.2	2.9 - 12.3	2.9 - 13.3	4.2 - 8.4	0.0 - 1.5
Mean Est. of Children-Occurrences	3,394,700	571,700	154,500	190,300	159,800	5,400
Percent of Total Child.-Occurrences	4.81	0.08	0.02	0.03	0.02	@
Mean Est. of Occurrences/Child Exposed	2.5	1.5	1.2	1.2	1.2	1.0

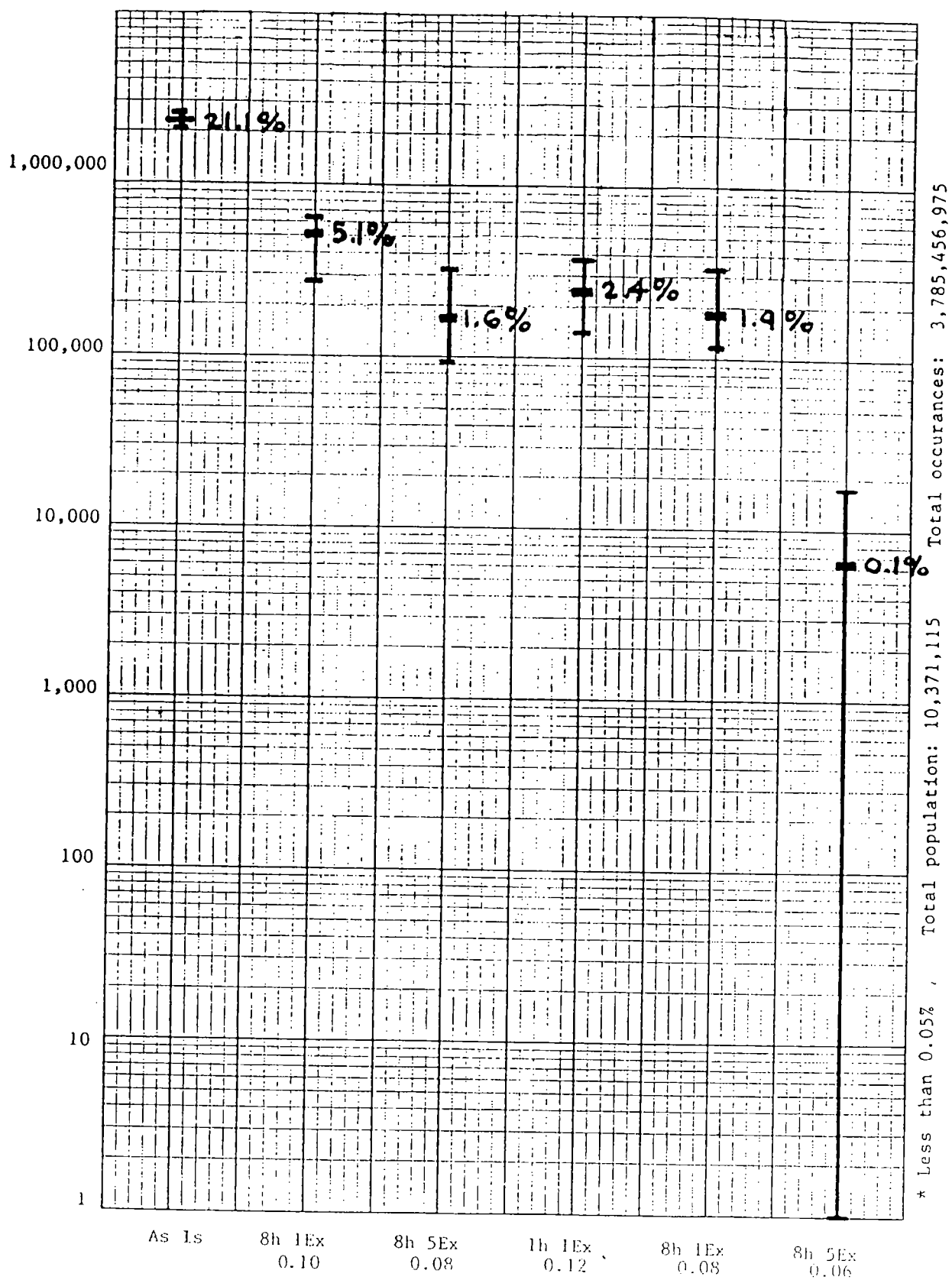
Notes:

^aEquivalent ventilation rate. It is equal to ventilation rate + body surface area; units are in $l \text{ min}^{-1} \text{ m}^{-2}$.

*Less than 0.05% but > 0.

@Less than 0.005% but > 0.

Figure 3. NUMBER OF PEOPLE IN LOS ANGELES WHO ARE EXPOSED ONE OR MORE TIMES PER YEAR TO 8H OZONE 0.06+ PPM @ 15 EVR OR HIGHER





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Office of Air Quality Planning and Standards
Research Triangle Park, North Carolina 27711

April 19, 1993

MEMORANDUM

SUBJECT: Testing pNEM/O₃ Runs to Determine if a Set of 10 Runs
is "Representative"

FROM: Tom McCurdy *Tom*
Ambient Standards Branch (MD-12)

TO: Ozone Team

Conclusion

The short conclusion derived from the analyses described below is that it is unlikely that using 10 runs of pNEM/O₃ will give systematically different results than if 100 or so runs are used. The range of estimates will always become larger when more runs are undertaken, but most exposure indices of interest are adequately represented by a 10-run sample. Selected 1h exposure variables may be exceptions to this conclusion.

Introduction

As you know, because of time and computer limitations we only provide exposure estimates for an area using a set of 10 runs. (More were used for CO, but that was a special situation.) Usually Monte Carlo (MC) modeling involves hundreds or even thousands of runs, so we certainly do not operate in a classic MC mode. A question always arises, therefore, about how representative is our small-size set of outputs. Related intuitive questions are:

- How "accurate" are the 10-sample estimates of central tendency and variance in the true MC "population" of pNEM runs?
- What is the true distribution of specific exposure indices?

Overview

I have undertaken a series of statistical tests on hypotheses related to these intuitive questions. Results of these tests are discussed below. In addition, information is presented regarding the distribution of selected important exposure indices.

All of the analyses discussed here are based upon 108 runs of pNEM/O₃ in Houston for the old "as is" air quality and population scenarios. The Houston case was used because pNEM/O₃ underwent a limited evaluation ("validation") in that city with generally favorable results.

Three population groups were investigated: children, outdoor workers, and everyone. Only the "entire population" results are discussed. Summary data are:

- population modeled: 2,266,825 in 567 cohorts
- total 1h and 8h daily maximum person-occurrences possible: 827,391,125 (population x 365 days in the O₃ season)
- total cohort-hours available for analysis of all non-exposure indices: 4,966,920 (this is a combination of the number of cohorts, districts, and hours in a year). This number forms the basis for OXMAX, PRODMAX, and other non-exposure variables that are defined below.

The 108 runs were divided into ten 10-run sets with 8 runs left over. The 10-runs sets were developed chronologically (for the most part) as they came out of the IBM mainframe. This is how a 10-run set would be obtained in practice.

For the record, each run took about 23 minutes of CPU time, and cost--in NCC funny money--about \$170. Thus, the total cost of the 108 runs is about \$18,400. All of the jobs were run overnight or on weekends at low priority to obtain the lowest per-CPU charges possible. Due to swapping in and out of the mainframe because of higher priority runs, elapsed time for a run often was an hour or more. Generally, only 3-4 runs could be obtained on any night.

Variables Investigated

The following air quality, ventilation, and exposure variables were investigated:

1. Air Quality

OX99.5: The 99.5 percentile O_3 cohort-hour exposure concentration. The value for outdoor microenvironments (μe) is obtained by "transforming" the nearest outdoor O_3 monitor via a regression-based multiplier and adding to it an error term (which may be negative). Indoor μe O_3 values are obtained via a mass-balance model, where air exchange rate is a very important variable.

There is little variability in OX99.5 in Houston--probably too little variability. The range is only 0.001 ppm (0.073-0.074 ppm). The coefficient of variability (COV, which is calculated by dividing the standard deviation [s.d.] by the mean [x] is only 0.5%. This is an extremely small COV.

OXMAX The maximum cohort-hour O_3 exposure concentration. The mean value of the 108 runs for this is 0.302 ppm, with a COV of 1.4%. Again, this is a very small COV. For comparison, the COV of the maximum O_3 concentration monitored in Houston for the same year being analyzed is 18.2% for 7 sites.

It should be noted that OXMAX as modeled is higher than the maximum monitored value. The highest OXMAX for the 108 runs is 0.315 ppm, whereas the highest monitored O_3 concentration is 0.28 ppm: an 11% difference. This difference is due to the error term linking monitor-to- μe concentrations. In a typical Houston pNEM/ O_3 run, less than 10 cohort-hour O_3 exposure estimates out of almost 5 million values are higher than an actual monitor concentration (<0.0002%).

The distribution of OXMAX for the 108 runs is depicted in Figure 1. It is a highly peaked nominally normal distribution.

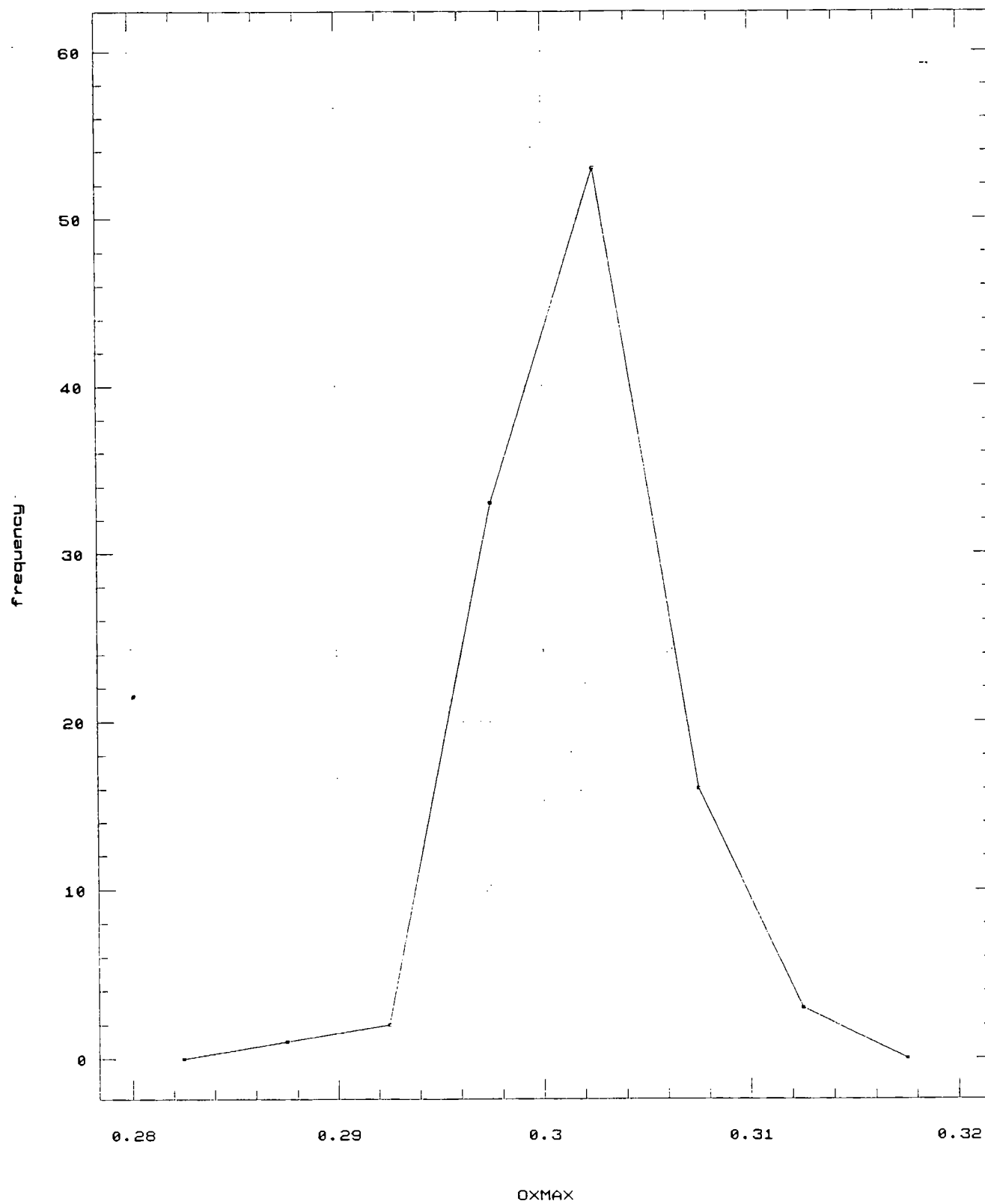
2. Ventilation Rate

VE99.5: The body-surface area adjusted ventilation rate (VE) for the cohort-hour in units of $l \min^{-1} m^{-2}$. For adults, VE is about one-half of the raw ventilation rate in $l \min^{-1}$. Mean VE99.5 for the 108 runs is $19.7 l \min^{-1} m^{-2}$. The COV for this variable is 0.02%, again an extremely small relative variation.

VEMAX: The maximum hourly-averaged VE experienced by any cohort in Houston. This value has a very small range in the 108 runs: $32.2 - 41.2 l \min^{-1} m^{-2}$. Its mean value is $35.4 l \min^{-1} m^{-2}$, and its COV is 5.7%. The distribution of VEMAX for the 108 runs is shown in Figure 2.

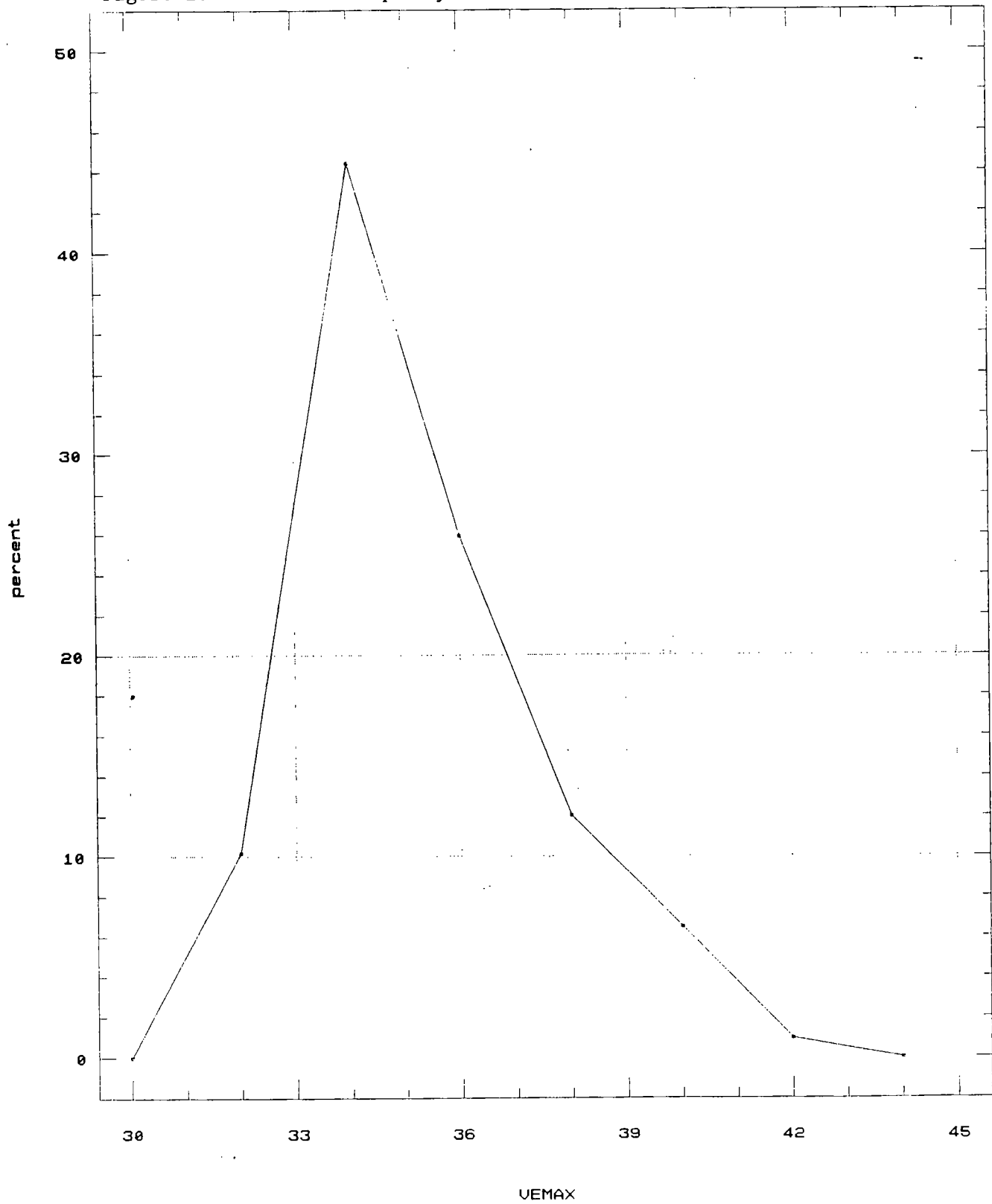
Frequency Polygon

Figure 1. Frequency Distribution of OXMAX



Relative Frequency Polygon

Figure 2. Relative Frequency Distribution of VEMAX



The small variability and low mean estimate for this variable resulted in my concern expressed to a number of you that pNEM/O₃ is systematically underestimating VEMAX. That concern is currently being investigated by IT-AQS. (We do have a "brake" on how high VE for any one hour can go in a pNEM/O₃ simulation. Perhaps this brake is not high enough to allow all possible VEs associated with athletes and maybe strenuous workers undergoing vigorous exercise. Determining what a reasonably high brake should be for hour-long strenuous exercise is the focal point of IT's current work.)

3. "Dose"

A surrogate for dose in pNEM/O₃ is the product of hour-specific VE and the O₃ exposure concentration estimated in each μ e for every cohort. This product is labeled PROD here.

PROD99: The 99th percentile of the calculated PROD values. The 108-run max, of PROD99 is 0.57 ppm l min⁻¹ m⁻², an unusual nomenclature. The COV for this variable is a small 1.9%.

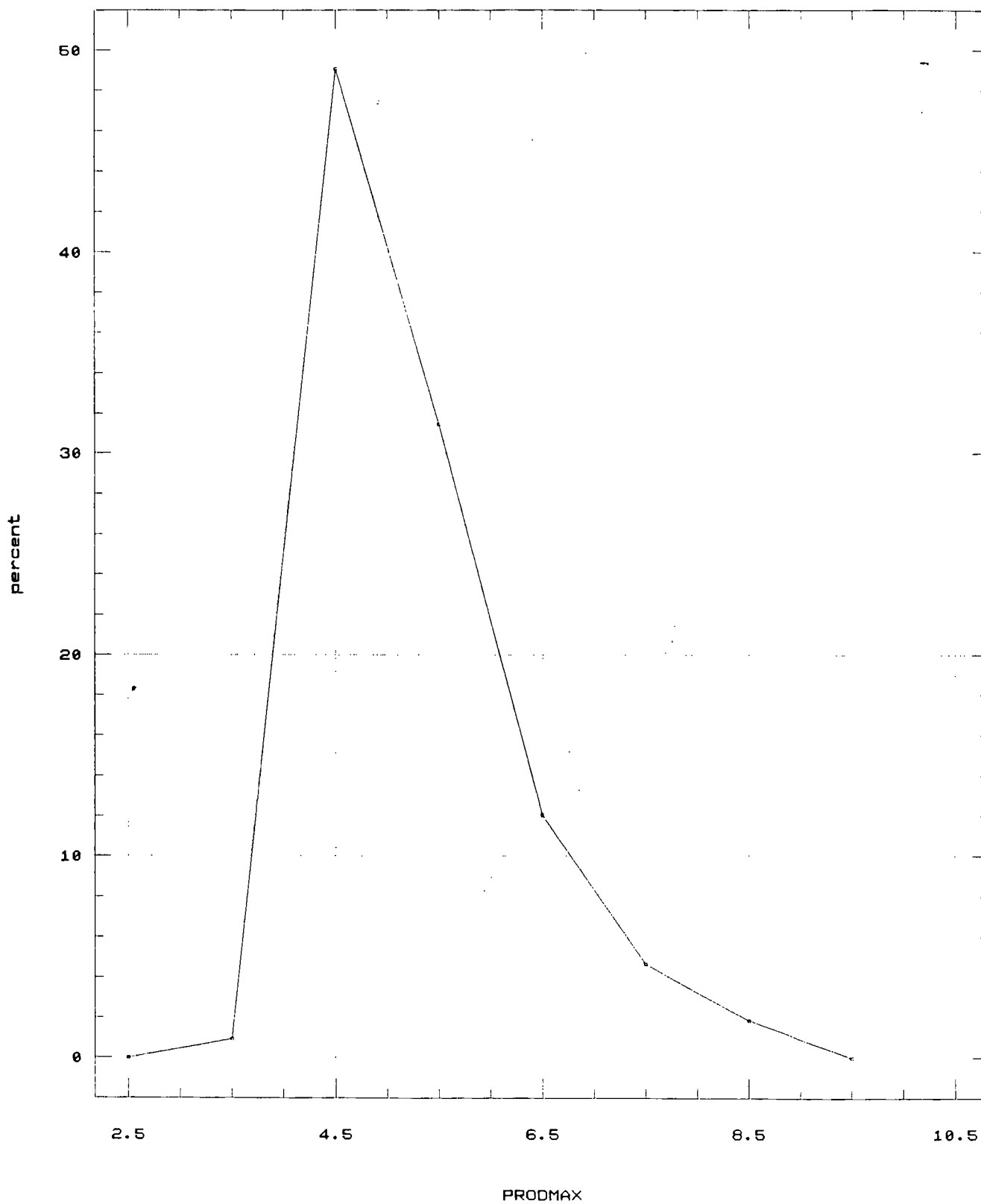
PROD99.5: As above, but for the 99.5th percentile value. Its mean is 0.70 ppm l min⁻¹ m⁻²--about 23% higher than PROD99. The COV for PROD99.5 is a very small 0.2%. It is unclear why PROD99.5 has a smaller COV than PROD99; in theory it should be larger. (PROD99.5 is further out on the distribution, and hence is inherently more variable. This should result in a greater COV.)

PRODMAX: The maximum hourly product of VE and O₃ concentration. The 108-mean of PRODMAX is 5.32 pmm l min⁻¹ m⁻². This value is almost 8 times higher than the mean PROD99.5 estimate. Its COV is a reasonable 17.5%. The distribution of PRODMAX for the 108 runs is depicted in Figure 3. It should be noted that PRODMAX is always less than the theoretically possible product of VEMAX and OXMAX. For a typical run, the following values are obtained:

OXMAX:	0.302 ppm
EVMAX:	33.2 l min ⁻¹ m ⁻²
PRODMAX:	5.89 ppm l min ⁻¹ m ⁻²

If OXMAX was multiplied by EVMAX, the resultant is 10.03 ppm l min⁻¹ m⁻², about 1-1/2 times higher than the actual PRODMAX. The reason for this, of course, is that OXMAX and EVMAX do not occur simultaneously during any single cohort-hour. This phenomenon is noted in all 108 runs and for all high-percentile values of the O₃, VE, and PROD distributions. It appears to be true

Figure 3. Relative Frequency Distribution of PRODMAX



for even low percentile values of the distributions, although the relative differences are much smaller than 1-1/2 times the actual product.

4. Exposure

Two types of exposure indices are presented. The first is the percentage of people who are estimated to experience one or more exposures above a specified daily maximum O_3 concentration level for an hour (or more) at a specified ventilation rate. The second is the percentage of total person-occurrences that are above a specified daily maximum O_3 concentration level for an hour (or more) at a specified ventilation rate. The abbreviation used for this exposure indicator is POC.

P1H25: The percentage of people (base = 4.97 million) who are estimated to "see" one or more 1h daily maximum O_3 exposures >0.12 ppm during an adjusted ventilation rate event (VE) of $25 \text{ l min}^{-1} \text{ m}^{-2}$ or higher. The mean p1H25 for the 108 runs is 2.4%, with a range of 0 - 7.5% for any individual run. The COV for this variable is 71.4%, probably a reasonable estimate. A histogram for p1H25 also is included as Figure 5.

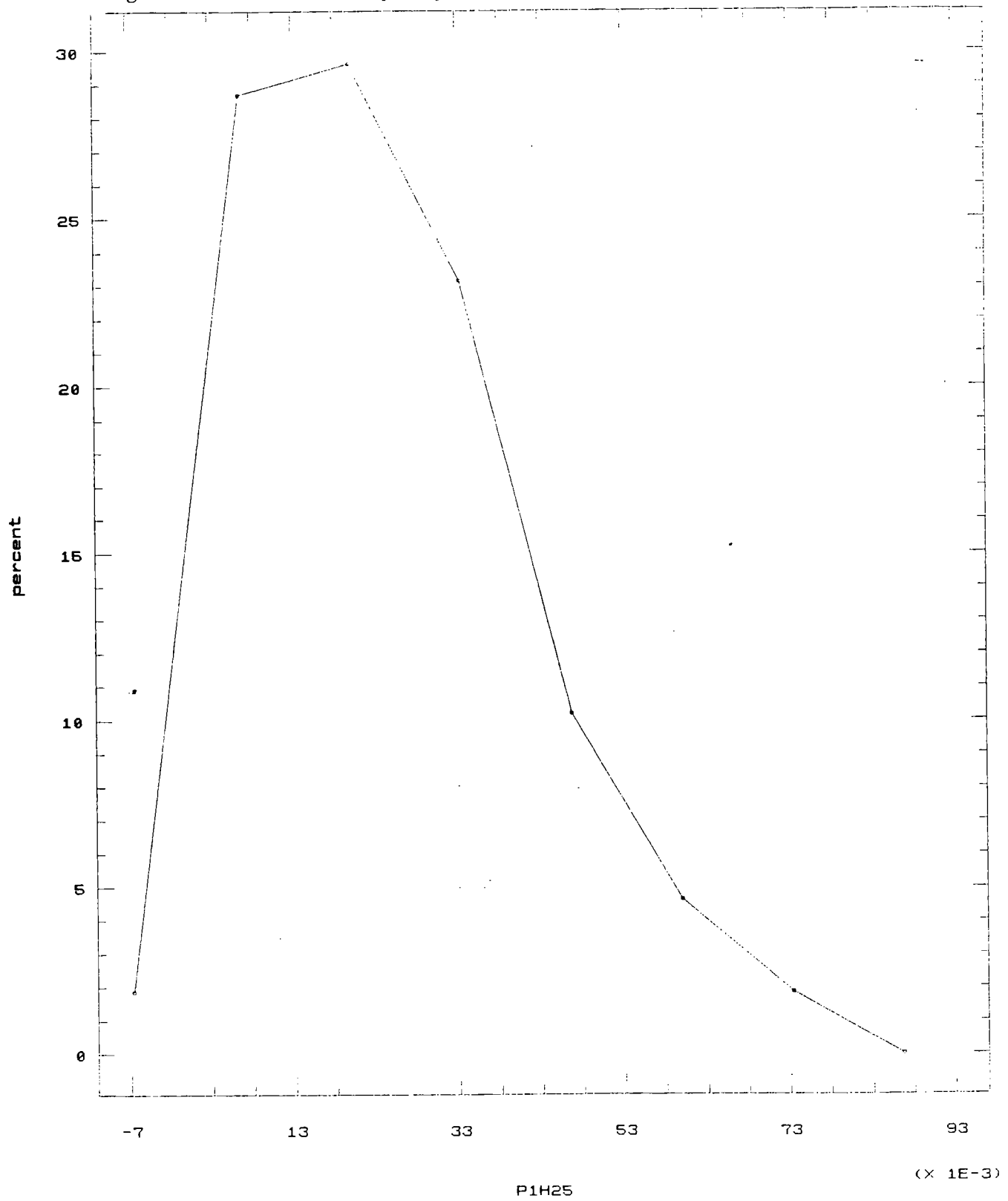
It should be noted that ASB is not really interested in 1h O_3 exposures at this low an EV. The EV of interest is $30 \text{ l min}^{-1} \text{ m}^{-2}$ for this averaging time, but every run had a 0 for this adjusted ventilation rate. (It was this unlikely result that started me to look more closely at the VE problem noted above under VEMAX.) Thus, as pNEM/ O_3 now stands, no one in Houston is exposed to O_3 above the current NAAQS level of 0.12 ppm during exercise at a level high enough to result in the types of FEV1 reductions and symptoms thought to be of concern. This is true even in an area with a "design value" for the year being analyzed of 0.19 ppm and having a maximum O_3 value of 0.28 ppm. A critic of the current O_3 NAAQS might say from this that there would be no health impacts from "actual" 1h exposures in Houston--at least for the year modeled (1982).

POC1H25: The percentage of total possible person-occurrences (base = 827.4 million) having an estimated daily maximum hourly O_3 exposure 0.12 ppm during a VE of $25 \text{ l min}^{-1} \text{ m}^{-2}$ or more. The mean POC1H25 is .007%, and its COV is 72.1%.

PER1EXP: This variable is the average number of times that a person who is exposed to $O_3 >0.12$ ppm is exposed to that concentration at an exercise level of $25 \text{ l min}^{-1} \text{ m}^{-2}$ or more. A PER1EXP of 1.0 means that the exposed person only experiences one 1h daily maximum exposure

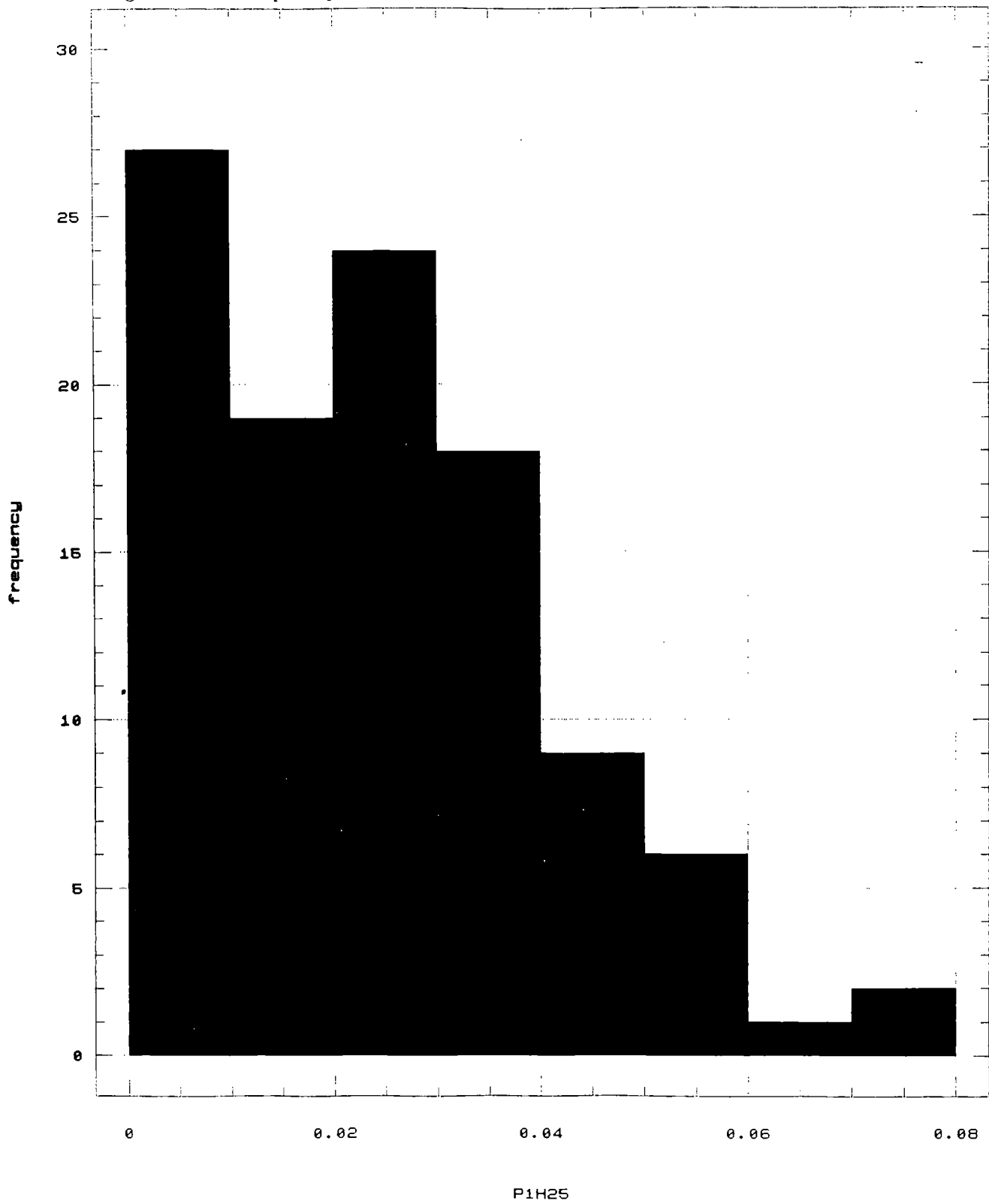
Relative Frequency Polygon

Figure 4. Relative Frequency Distribution of P1H25



Frequency Histogram

Figure 5. Frequency Distribution of P1H25



during the entire O₃ season. (In Houston, this is the entire year.) The max PER1EXP for the 108 runs is 1.04, or slightly above 1/year. The maximum is 1.78 or almost 2/year. The distribution of PER1EXP is shown in Figure 6 for the 108 run data set.

This variable needs some elaboration. It is obtained thusly:

$$\text{PER1EXP} = (\text{POC1H25} * 827,391,125) / (\text{P1H25} * 2,266,825)$$

for only those cases where P1H25 (and POC1H25) >0. Thus, it represents the average number of 1h daily maximum exposures seen by an "exposed person" (in this case, to an exposure of >0.12 ppm at a ventilation rate of 25 l min⁻¹ m⁻² or more). This variable "hides" the fact that some exposed people can experience many exposures, while the majority may see only one exposure. Of course, this is only true if PER1EXP >1 for any individual run.

For the 107 runs with a P1H25>0, PER1EXP = 1 in 55 of the runs (51.4%). In the remaining 52 runs, some cohorts experienced 2 or more exposures at the circumstances of interest but only the average number of exposures/exposed person are able to be calculated currently. A different output format could provide exact estimates of the number of people who experience 1, 2, n numbers of exposures at any "cutpoint" concentration or exercise level (ventilation rate), but these data are not now available.

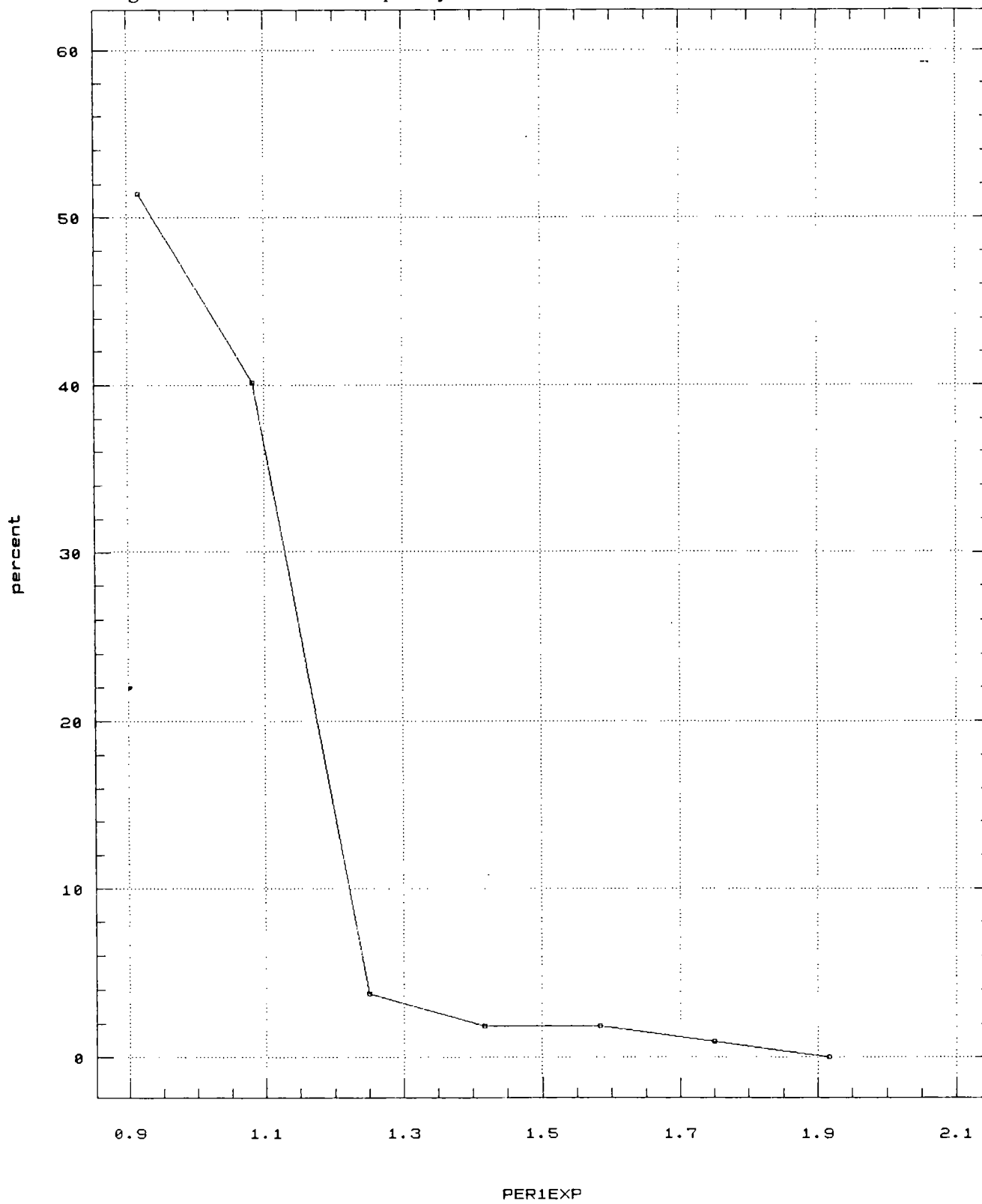
P8H06: The percentage of people who "experience" one or more 8h daily maximum (DM) O₃ exposures >0.06 ppm at a ventilation rate of 15 l min⁻¹ m⁻² or higher.

Every run has someone at this critical exposure/ventilation combination. The mean percentage estimate for the 108 runs is 3.9%, and the range is 0.5-9.9%. The COV for this variable is a reasonable 51.8%.

Since no one in Houston experiences a 1h DM exposure at >0.12 ppm at high exercise ($\geq 30 \text{ l min}^{-1} \text{ m}^{-2}$), the 8h DM exposure estimate noted above obviously is the controlling exposure metric if a comparison between 0.06 ppm 8h DM and 0.12 ppm 1h DM impacts is of interest. Since this statement is true of the other two 8h DM evaluated below, it won't be mentioned again.

Relative Frequency Polygon

Figure 6. Relative Frequency Distribution of PER1EXP



POC8H06: POC for 8h DM >0.06 ppm at a VE of $15 \text{ l min}^{-1} \text{ m}^{-2}$ or more. The mean value for this variable is 0.012% and its COV is 57.7%.

The average number of times that a person is exposed to 0.06 ppm 8h DM at the ventilation rate noted above (PER8EX06) is 1.1/year. This varies between 1.0 and 2.4 for the 108 runs.

P8H08: The percentage of people who "see" one or more 8h DM O_3 exposures >0.08 ppm at a ventilation rate of $15 \text{ l min}^{-1} \text{ m}^{-2}$ or more.

The range of P8H08 in the 108 runs is 0 - 5.2%. Five runs (4.6%) have no one at this critical exposure combination. The mean estimate of the variable is 1.4%, and the COV is 88.7%. The distribution of P8H08 in the 108 runs is shown in Figure 7.

POC8H08: The POC for 8h DM >0.08 ppm at a VE of $15 \text{ l min}^{-1} \text{ m}^{-2}$ or higher. The mean of this variable is 0.004%, and its COV is 92.3%.

The average number of times that a person is exposed to the above exposure/ventilation combination (PER8EX08) is 1.1 times/year for the 103 runs with a non-zero outcome. PER8EX08 varies between 1 and 1.9.

P8H10: Only 70 of the runs (65%) has anyone in this combination exposure/ventilation category. The mean of P8H10 is 0.5%, including all of the runs with no exposure. The COV for this variable is 162.5%--probably a reasonable estimate for this inherently extreme exposure indicator.

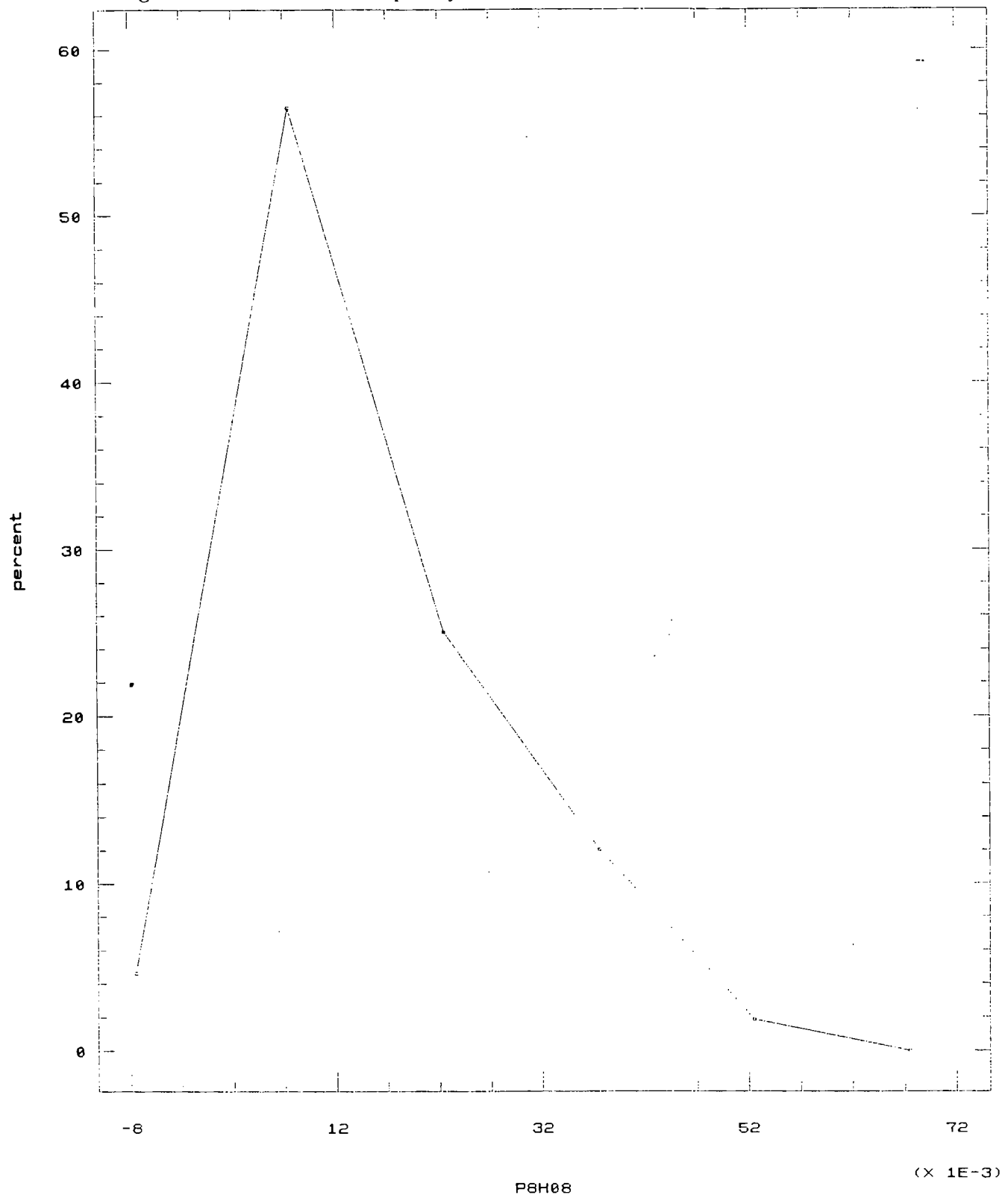
POC8H10: The POC for 8h DM >0.10 ppm at an VE of $15 \text{ l min}^{-1} \text{ m}^{-2}$. The mean of POC8H10 is 0.0014%, and its COV is 164.5%.

The average number of times per year that a person is exposed to 8h DM >0.10 ppm if they are exposed at all (PER8EX10) is 1.0 for the 70 runs with a non-zero outcome. Like PER8EX08, PER8EX10 varies between 1 and 1.9 for individual runs.

PAVE: The percentage of people with an 8hDM seasonal (April through October) mean >0.036 ppm. The mean estimate is 2.0%, and the 108-run range is between 0.04-2.8%. The COV of PAVE is 2.2%. The distribution of PAVE is depicted in Figure 8.

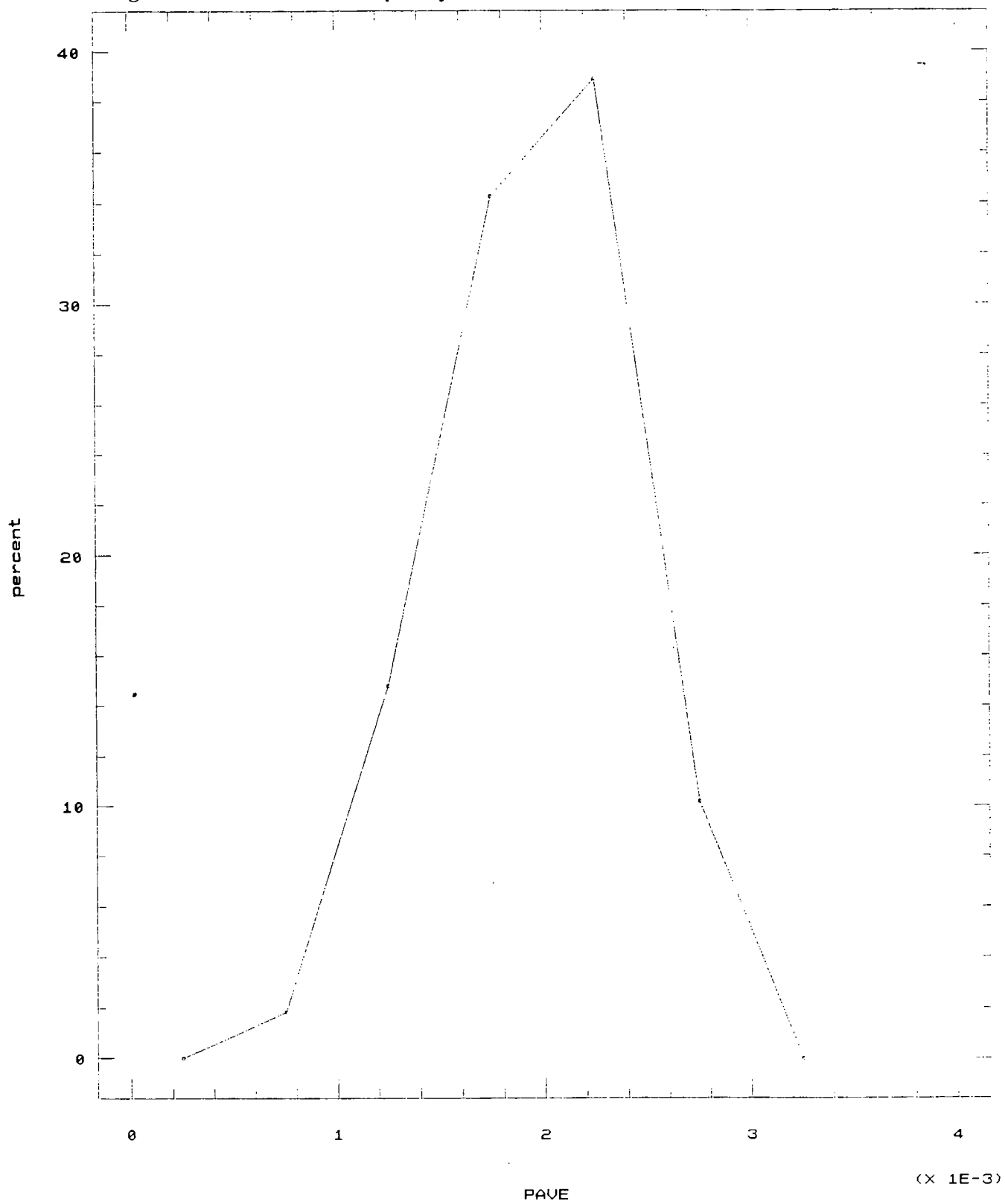
Relative Frequency Polygon

Figure 7. Relative Frequency Distribution of P8H08



Relative Frequency Polygon

Figure 8. Relative Frequency Distribution of PAVE



This concludes the descriptive statistical part of this memo. Most of the results seem logical with the exception of the ventilation indices--and, therefore, the dose indices dependent upon them. With respect to the 8h DM exposure indicators, the following mean results for Houston are obtained:

8h DM Cutpoint*	Percent of Population Exposed	Percent of Total Person- Occurrences
>0.06	3.9	0.0123
>0.08	1.4	0.0041
>0.10	0.5	0.0014

*During a ventilation rate of $>15 \text{ l min}^{-1} \text{ m}^{-2}$ or higher.

This is for an area with an 8h DM "design value" of 0.15 ppm (and an 1h DM design value of 0.19 ppm). Clearly the 8h exposures are more important than the 1h exposures in Houston since pNEM/O₃ predicts that no one will be exposed to 0.12 ppm O₃ at exercise levels shown to be harmful ($>30 \text{ l min}^{-1} \text{ m}^{-2}$).

We turn next to statistical tests of hypotheses regarding samples of 10 runs taken from the total set of 108 runs. An overview of hypothesis testing introduces this work.

Hypothesis Testing

In the strict sense, hypothesis testing involves using data from one or more samples to support or deny a statement regarding the entire population of interest. To make valid inferences from most statistical tests the samples usually have to be independent and random. In addition, the variable being tested should be normally distributed. Non-parametric tests can be used when the data are not normally distributed. In fact, non-parametric tests are more appropriately known as "distribution-free tests."

It is clear that sets of pNEM/O₃ runs do not represent independent and random samples. Each pNEM/O₃ run represents the output of a complex simulation model; it is not a datum point that can be observed. Thus, strictly speaking we cannot do statistical hypothesis testing of pNEM/O₃ (or any other model) outputs. This conclusion, however, leaves us no where to go if we want to understand the representativeness of sets of pNEM/O₃ compared to a full-blown Monte Carlo exercise involving hundreds

or thousands of runs. Therefore, for purposes of this memo, results of each pNEM/O₃ run for a specified indicator (variable) are treated as a simple observation from some unknown population. Sets of these runs are treated as an independent and random sample from this unknown population. The sampling scheme involves 10 sets of 10 independent observations (runs) and 1 set of 98 observations that excludes the set of 10 observations being tested. The population of interest is an infinite-sized group of pNEM/O₃ outputs, each containing the entities (the indicator variable). Inferences will be made to this population of pNEM/O₃ runs.

Defined this way, we have an identified population of interest and independent sampling. We still do not have random sampling in the strict sense. It is non-random in that I put pNEM/O₃ into discrete sets of 10 runs roughly based upon their "order of exit" from the mainframe computer. It is random in that this order should make no systematic impact on any particular variable (observation) since each variable is predicated upon Monte Carlo sampling--itself a random process. For purposes of this memo, I consider this to be adequate justification of a random sample.

That leaves the question of normality of the variable's distribution. Explicit tests of each variable's distribution can be rather easily done, but an adequate indication of normality is obtained by evaluating standardized skewness and kurtosis statistics for each variable. Most variables in the pNEM/O₃ outputs are not normally distributed using these statistics. Therefore, we shall use a comparison of sample distributions (a set of 10 versus another set or the "full" 98 run sample: see above) to evaluate statistical similarity. Specifically, I will use Kolmogorov-Smirnov (K-S) two-sample nonparametric test. The principle behind this test is simple:

If the null hypothesis that independent random samples have been drawn from identical populations is correct, then we would expect the cumulative frequency distributions for the two samples to be essentially similar. The test statistic...is the maximum difference between the two cumulative distributions. If the maximum difference is larger than would be expected by chance under the null hypothesis, this means the gap between the distributions has become so large that we decide to reject the hypothesis (H. Blalock, Social Statistics, p. 203).

This test will be backed up by the classic difference-in-means test even though it requires an assumption of normally distributed variables. If the null hypothesis (H_0) can be rejected on both tests, I am very confident that the samples for the variable being evaluated come from different populations.

Results of the Hypotheses Testing

Eleven indicator variables were tested, each one being represented by 10 independent sets of data. Thus, 110 Difference-in-Means and K-S tests were performed, or 220 tests total. Box plots show the variability in the set distributions for 3 variables. These plots are presented as Figures 9-11. Figure 9 depicts the set distributions (when a set is identified by an INDEX number) for OXMAX. Note that there is a set #11, but that is the "left-over" group of 8 runs; ignore its data.

There is variability in OXMAX among the sets. Set 6 has little spread, whereas set 4 has a wide spread. When OXMAX is tested using the two hypotheses tests described above, the K-S indicates that set 6 may come out of a different population than all of the others ($D_m = 0.46$, $p = 0.044$). See Table 1 for a listing of "Rejected H_0 " sets. The K-S test confirms that the set 6 (cumulative frequency) distribution, or cfd, is different than the others taken as a whole. Note that Set 6 does not show up as being different when a difference-in-means test is used; see Table 1. However, Set 9 does show up as being statistically different using this test (more formally the H_0 that $\mu_1 = \mu_2$ for Set 6 versus all other runs as a group is rejected (t -test = 2.57, $p = 0.011$)).

The set spread for P1H25 is depicted in Figure 10. There is a lot of spread in this variable for all sets (ignore INDEX 11). The K-S test of this variable indicates that Set 8 is statistically different than the others as a whole ($D_m = 0.48$, $p = 0.031$). Sets 8 and 9 both "flunk" using the difference-in-means test. In fact, P1H25, and its person-occurrences version (POC1H25), are the only indices that have any set being rejected using both hypotheses-testing tests. That set is INDEX 8.

The set variability for variable P8H08 is depicted in Figure 11. When formally tested, Set 7 appears to be different than the remainder, using the K-S ($D_m = 0.432$, $p = 0.025$), but not the difference-in-means test. Set 7 also fails the K-S test for POC8H08 ($D_m = 0.456$, $p = 0.021$).

The other variables that were tested appear in Table 1. For the more-appropriate K-S test, note that no set is rejected on more than one indicator variable. Thus, there does not seem to be a systematic structure to the rejected sets. It is possible, therefore, to choose a quasi-random set of 10 pNEM/O₃ runs and get an atypical result to a particular variable than if 100 runs were used to illustrate that variable. That set, however, probably will not be atypical for all variables of interest.

I also tested individual sets of 10 against each other rather than against the 98 other runs as a set. It is easy to reject H_0 of no difference-in-cfd for two individual sets of 10.

Multiple Box-and-Whisker Plot

Figure 9. Box Plots of OXMAX

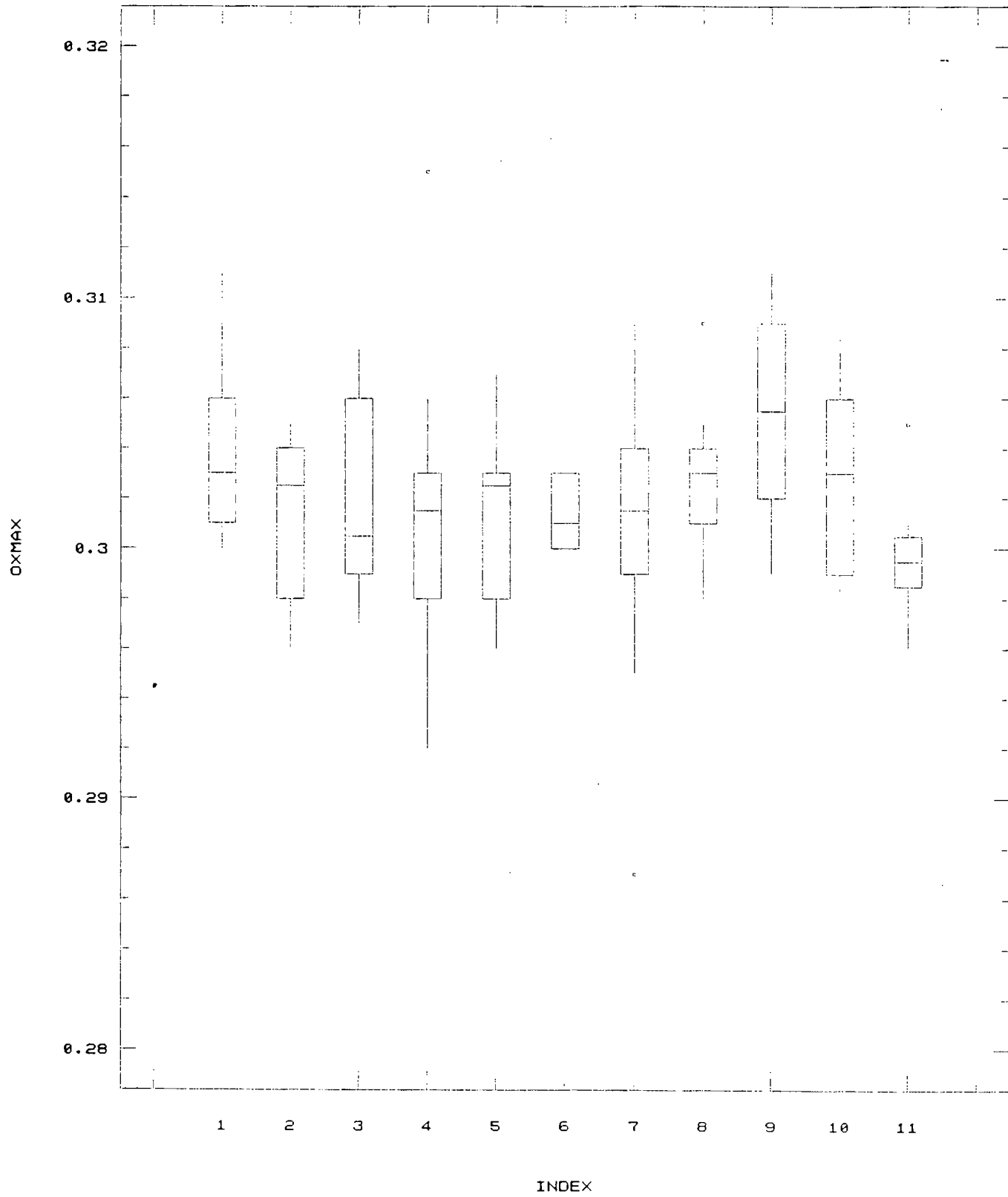


Table 1

SUMMARY TABLE OF HYPOTHESES TESTING: IDENTIFYING SETS
WHERE H_0 IS REJECTED AT A $p \leq 0.05$

Indicator Variable	Difference- in-Means Test ¹	K-S Non-parametric Test ²
OXMAX	Set 9	Set 6
PRODMAX	None	None
P1H25	Sets 8 & 9	Set 8
POC1H25	Sets 3, 8, & 9	Set 8
P8H06	None	Set 5
POC8H06	None	None
P8H08	None	Set 7
POC8H08	None	Set 7
P8H10	None	Set 9
POC8H10	None	Set 9
PAVE	None	None

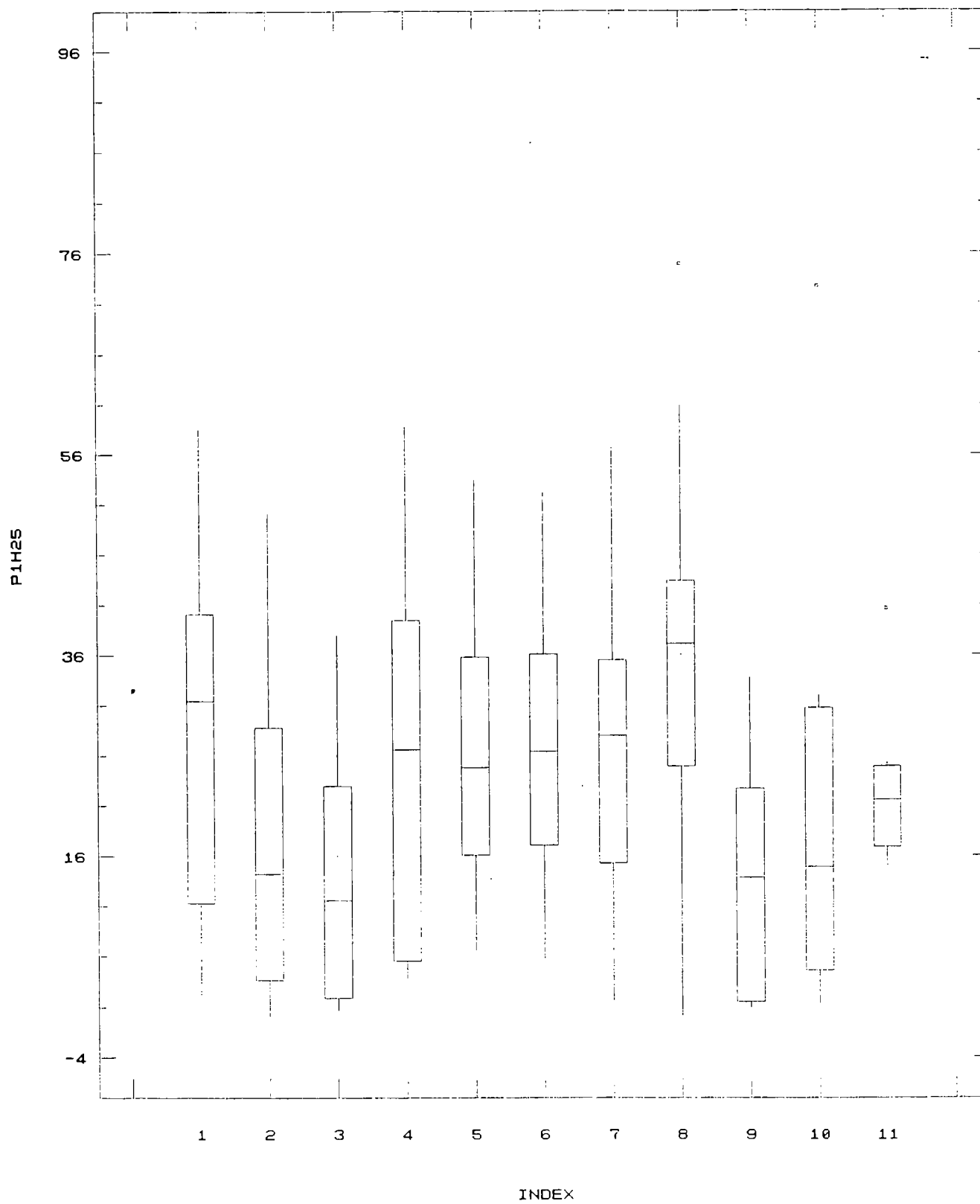
Notes: (1) $H_0: \mu_1 = \mu_2$
 $n: n_1 = 10; n_2 = 98$
test stat: t-test
 $\alpha: \leq .05$

(2) $H_0: cfd_1 = cfd_2$
 $n: n_1 = 10; n_2 = 98$
test stat: $D_m (\chi^2)$
 $\alpha: \leq .05$

Multiple Box-and-Whisker Plot

(× 1E-3)

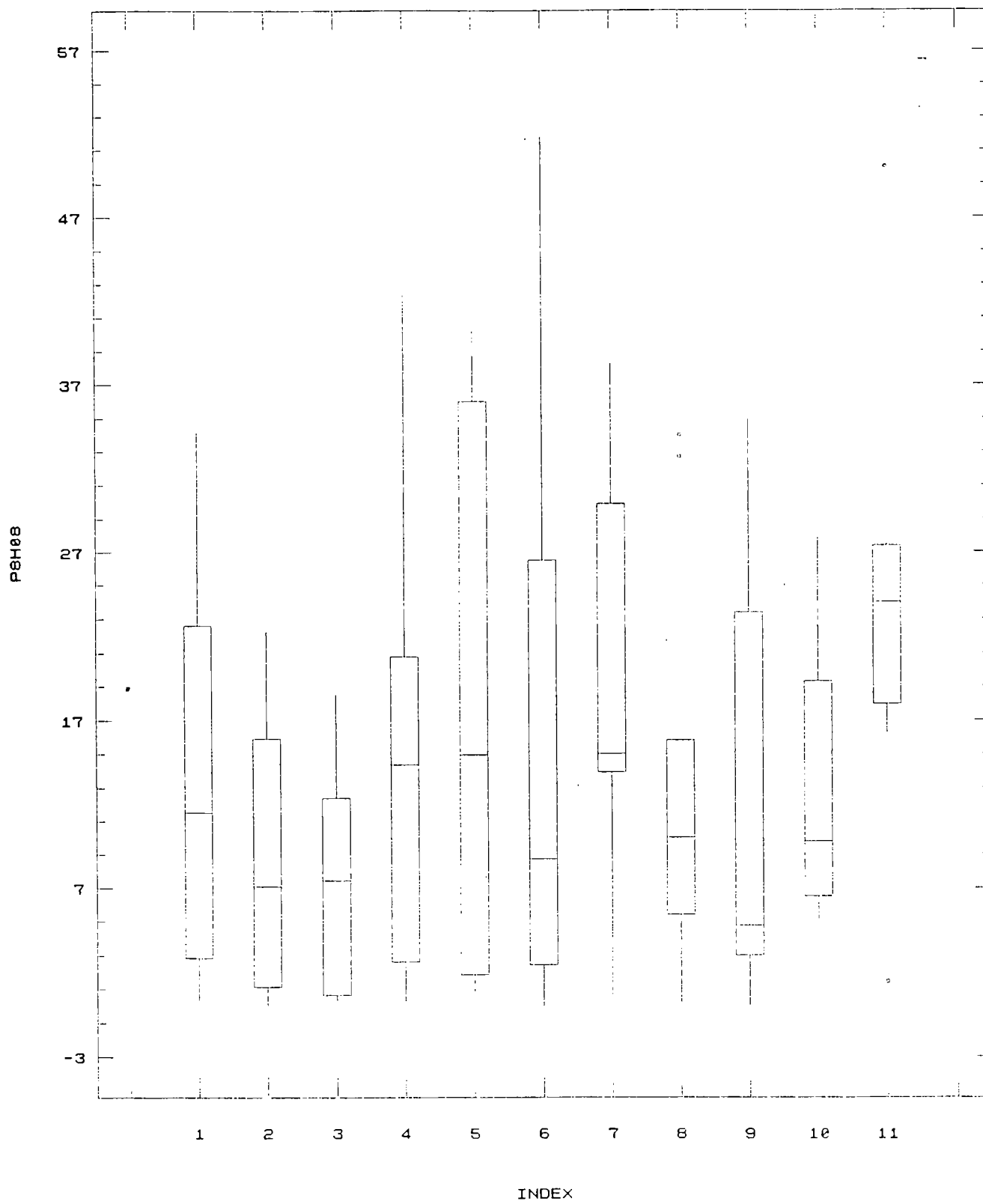
Figure 10. Box Plots of P1H25



Multiple Box-and-Whisker Plot

(× 1E-3)

Figure 11. Box Plots of P8H08



For instance, most of the exposure indices are different using the K-S test on sets 3 and 7. Set 7, however, is only different from the 98-run set for two indicator variables using the K-S test (P8H08 and POC8H08). Set 3 is not different from the 98-run set for any variable. Thus, individual sets of 10 may be significantly different from each other, but usually are not different than the group as a whole.

This concludes this memo. If you have any questions regarding the work discussed here, please call me soon* at 541-5658. (*Otherwise, I'll forget what I did.)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Office of Air Quality Planning and Standards
Research Triangle Park, North Carolina 27711

February 17, 1994

Dr. George T. Wolff, Ph.D.
Principal Scientist
General Motors Corporation
Environmental & Energy Staff
Argonaut A-205-H
485 W. Milwaukee
Detroit, Michigan 48202-3220

Dear Dr. Wolff:

As discussed at the December 16, 1993 meeting of the Clean Air Scientific Advisory Committee's (CASAC's) Subcommittee on ozone (O₃) Exposure and Risk, the next meeting of the Subcommittee on March 24 will focus on the health risk assessment methodology. To facilitate the discussion, I am transmitting the enclosed materials directly to you and the Subcommittee members.

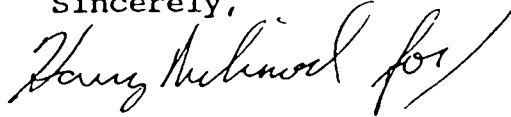
The document, A Probabilistic Assessment of Health Risks Associated With Short- and Long-Term Exposure to Tropospheric Ozone, dated February 1994, describes in detail the health risk assessment methodology that the Ambient Standards Branch proposes to use in the O₃ national ambient air quality standards review. The report was prepared by Argonne National Laboratory under an interagency agreement with the Environmental Protection Agency.

The draft report builds on earlier O₃ health risk assessment efforts conducted over the last 8 years. Work is still underway to expand the assessment to include airway reactivity as a health endpoint associated with 8-hour exposures and to explore the feasibility of assessing certain inflammatory indicators, using the results from bronchoalveolar lavage studies. While we plan to address these additional endpoints at the March 24 meeting, these endpoints are not included in the current draft document.

Similar to the review of the exposure assessment methodology reports, we request that Subcommittee members review the draft document to provide us with specific advice and recommendations as to the technical soundness of the health risk methodology. In order to avoid delays later in the review process, we must identify now any areas in the methodology that require further refinement.

Thank you for agreeing to participate in this review. We look forward to receiving the Subcommittee's comments and recommendations at the March meeting. By copy of this letter, I am also forwarding the enclosed report to the members of the CASAC for their information.

Sincerely,

A handwritten signature in cursive script, appearing to read "Karen M. Martin", followed by a large, sweeping flourish.

Karen M. Martin, Ph.D.
Chief
Ambient Standards Branch

Enclosure

cc: S. Ayres
R. Bond
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S. Colome
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J. Price
F. Speizer
M. Utell
P. Ward

Draft — Do Not Cite or Quote

**A PROBABILISTIC ASSESSMENT OF HEALTH RISKS ASSOCIATED WITH
SHORT- AND LONG-TERM EXPOSURE TO TROPOSPHERIC OZONE**

prepared for

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U.S. Environmental Protection Agency
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February 1994

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CONTENTS

ACRONYMS, INITIALISMS, AND ABBREVIATIONS	xi
DISCLAIMER	xii
ABSTRACT	1-1
1 INTRODUCTION	1-1
1.1 Background	1-2
1.2 Risk Assessment Approach	1-3
1.3 Report Organization	1-5
2 EXPOSURE MODEL	2-1
2.1 EXPOSURE MODELING METHODOLOGY	2-2
2.1.1 Define the Study Area, Subdivisions of the Study Area, the Exposure Period and the Population-of-interest	2-2
2.1.2 Divide the Population-of-Interest Into an Exhaustive Set of Cohorts	2-3
2.1.3 Develop an Exposure Event Sequence for Each Cohort for the Exposure Period	2-3
2.1.4 Estimate the Pollutant Concentration and Ventilation Rate Associated With Each Exposure Event	2-4
2.1.5 Extrapolate the Cohort Exposures to the Population of Interest and to Individual Sensitive Groups	2-5
2.2 Exposure Estimates Used in the Risk Assessment	2-5
2.3 Alternative Air Quality Scenarios Included in the Analysis	2-6
3 HEALTH EFFECTS DATA AND JUDGMENTS	3-1
3.1 Criteria for Selecting Laboratory Data	3-1
3.2 1-Hour Exposure-Response Relationships for Heavily Exercising Populations	3-1
3.3 1-Hour Exposure-Response Relationships for Moderately Exercising Populations	3-4
3.4 8-Hour Exposure-Response Relationships	3-6
3.5 Seasonal Exposure-Response Relationships	3-8

CONTENTS (Cont'd)

4 MODELING TECHNIQUES	4-1
4.1 Correcting FEV Decrement Calculations for the Effects of Exercise in Clean Air	4-1
4.2 Developing Probability Distributions at Desired Exposure Levels for Acute Endpoints	4-3
4.3 Developing Exposure-Response Relationships for Chronic Health Endpoints	4-20
5 RISK MODEL	5-1
6 A DESCRIPTION OF RISK RESULTS	6-1
REFERENCES	R-1
APPENDIX A: RISK ESTIMATES FOR SELECTED HEALTH ENDPOINTS	A-1

TABLES

2.1 Ozone Seasons for the Nine Urban Areas	2-3
2.2 Ozone Concentration Intervals (ppm) for which pNEM/O ₃ Data Have Been Generated	2-7
2.3 Ozone Concentrations (ppm) at which Responses Rates Need to be Estimated	2-8
2.4 Calculating Exposure Probabilities for pNEM/O ₃ Person-Occurrences Estimates	2-9
2.5 Definitions of the Six Alternative Air Quality Scenarios	2-10
3.1 Health Endpoints Associated with each Study	3-2
3.2 Summary of Studies Used in Developing 1-hour Exposure-Response Relationships for Heavily Exercising Individuals	3-4
3.3 Summary of the Study Used to Develop 1-hour Exposure-Response Relationships for Moderately Exercising Populations	3-6

TABLES (Cont'd)

3.4	Summary of Studies Used to Develop 8-Hour Exposure-Response Relationships . .	3-8
4.1	FEV Data from McDonnell et al. (1991) - Subject 12	4-2
4.2	Summary of Experimental Data — Forced Expiratory Volume	4-9
4.3	Summary of Experimental Data - Symptoms	4-10
4.4	Exposures at which Responses Need to be Estimated	4-11
4.5	Estimates of Parameters and Associated r^2 Values	4-12
4.6	Estimates Regarding DFEVC $\geq 10\%$ for the 6.6 Hour Studies	4-14
4.7	Number of Subjects Used (N) in Developing Probabilistic Exposure-Response Relationships	4-15
4.8	Probability Distributions Over the Percentage of the Population Having DFEVC $\geq 10\%$ (6.6 hr exposures)	4-16
4.9	Tabular Version of Expert A's Judgments About Percentage Response Rates at Ozone Concentrations Needed for the Risk Calculations (mild lesions, Los Angeles, children, 1 season)	4-23
5.1	Calculating the Median of the Response Rate Distribution	5-2
6.1	Probability Distributions Over Person-Occurrences of FEV $\geq 10\%$	6-2

FIGURES

1.1	The Risk Model Includes an Exposure Model and Health Model	1-3
1.2	Relationships Between Benchmark and Headcount Risk Models	1-4
2.1	Major Components of the NEM Series of Exposure Models and Associated Health Risk Assessment Procedures	2-1
4.1	Effects of an Increase in Forced Expiratory Volume in Clean Air	4-6
4.2	Effects of a Decrease in Forced Expiratory Volume in Clean Air	4-7

FIGURES (Cont'd)

4.3	Method to Estimate Response Rates for Acute Effects at Desired Ozone Concentrations.	4-8
4.4	Medians and 90% CIs for Four 1-Hr Health Endpoints	4-17
4.5	Medians and 90% CIs for Four 8-Hr Health Endpoints	4-18
4.6	Medians and 90% CIs for Two 8-Hr Health Endpoints	4-19
4.7	Encoded Judgments of Expert A (mild lesions, children, Los Angeles, 1 season)	4-21
4.8	Judgments of Expert A in Exposure-Response Format	4-21
4.9	Judgments of Expert A Adjusted to pNEM/O ₃ Exposure Concentrations	4-22
6.1	Risk Results for Two Air Quality Scenarios	6-3
6.2	Representative Distributions for 6 Air Quality Scenarios	6-3
6.3	Comparison of FEV $\geq$ 10%, 1-Hr Exposures, As-Is Results Based on Data from Three Clinical Studies	6-4
6.4	Risk Distributions for Mild Lesions Based on the Judgments of Expert A	6-5
6.5	Representative Risk Distributions for Expert A	6-6
A.1	Risk Distributions for FEV Decrements $\geq$ 10% Based on Data from the Avol et al. (1984) Study	A-5
A.2	Risk Distributions for FEV Decrements $\geq$ 10% Based on Data from the Kulle et al. (1985) Study	A-6
A.3	Risk Distributions for FEV Decrement $\geq$ 10% Based on Data from the McDonnell et al. (1983) Study	A-7
A.4	Risk Distributions for FEV Decrement $\geq$ 10% Based on Data from the Seal et al. (1993) Study	A-8
A.5	Risk Distributions for FEV Decrement $\geq$ 15% Based on Data from the Avol et al. (1984) Study	A-9

FIGURES (Cont'd)

A.6 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the Kulle et al. (1985) Study	A-10
A.7 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the McDonnell et al. (1983) Study	A-11
A.8 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the Seal et al. (1993) Study	A-12
A.9 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the Avol et al. (1984) Study	A-13
A.10 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the Kulle et al. (1985) Study	A-14
A.11 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the McDonnell et al. (1983) Study	A-15
A.12 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the Seal et al. (1993) Study	A-16
A.13 Risk Distributions for Any Cough Based on Data from the Kulle et al. (1985) Study	A-17
A.14 Risk Distributions for Any Cough Based on Data from the McDonnell et al. (1983) Study	A-18
A.15 Risk Distributions for Any Cough Based on Data from the Seal et al. (1993) Study	A-19
A.16 Risk Distributions for Any Chest Discomfort on Data from the Kulle et al. (1985) Study	A-20
A.17 Risk Distributions for Any Chest Discomfort Based on Data from the McDonnell et al. (1983) Study	A-21
A.18 Risk Distributions for Any Lower Respiratory Symptoms Based on Data from the Avol et al. (1984) Study	A-22
A.19 Risk Distributions for Moderate/Severe Cough Based on Data from the Kulle et al. (1985) Study	A-23

FIGURES (Cont'd)

- A.20 Risk Distributions for Moderate/Severe Cough Based on Data from the McDonnell et al. (1983) Study
- A.21 Risk Distributions for Moderate/Severe Chest Discomfort Based on Data from the Kulle et al. (1985) Study
- A.22 Risk Distributions for Moderate/Severe Chest Discomfort Based on Data from the McDonnell et al. (1983) Study
- A.23 Risk Distributions for Moderate/Severe Lower Respiratory Symptoms Based on Data from the Avol et al. (1984) Study
- A.24 Risk Distributions for FEV Decrement $\geq 10\%$ Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies
- A.25 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies
- A.26 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies
- A.27 Risk Distributions for Any Cough Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies
- A.28 Risk Distributions for Shortness of Breath Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies
- A.29 Risk Distributions for Pain on Deep Inspiration Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies
- A.30 Risk Distributions Expert A, Mild Lesions, Los Angeles, Children, 1 Season, All Air Quality Scenarios
- A.31 Risk Distributions for Expert A, Mild Lesions, Los Angeles, Children, 10 Seasons, All Air Quality Scenarios
- A.32 Risk Distributions for Expert A, Moderate Lesions, Los Angeles, Children, 1 Season, All Air Quality Scenarios

FIGURES (Cont'd)

A.33 Risk Distributions for Expert A, Moderate Lesions, Los Angeles, Children, 10 Seasons, All Air Quality Scenarios	A-37
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ACRONYMS, INITIALISMS, AND ABBREVIATIONS

ACF	any cough
ACH	any chest discomfort
ALR	any lower respiratory symptom
ANL	Argonne National Laboratory
BRT	shortness of breath
CD	criteria document
CI	credible interval
DFEV	decrease in forced expiratory volume
DFEVC	decrease in forced expiratory volume corrected for exercise in clean air
ECAO	Environmental Criteria and Assessment Office
EES	exposure event sequence
ELPM	equivalent ℓ/min (ventilation rate adjusted for [i.e., divided by] body surface area, which is typically assumed to be 1.9 m^2 for adults; the units are $\ell/\text{min}\text{-m}^2$)
EPA	U.S. Environmental Protection Agency
FEV	forced expiratory volume - the maximum amount of air that can be expelled from the lungs in 1 second
GCU	geographical census unit
MCF	moderate/severe cough
MCH	moderate/severe chest discomfort
MLR	moderate/severe lower respiratory symptom
NAAQS	national ambient air quality standard
NEM	NAAQS exposure model
O ₃	ozone
OAQPS	Office of Air Quality Planning and Standards
ppm	parts per million
PDI	pain on deep inspiration
pNEM/O ₃	probabilistic NAAQS exposure model for ozone
ScnASIS	as-is air quality scenario
Std1112	current ozone NAAQS: 1-hr averaging time, 1 expected exceedance, 0.12 ppm ozone

ACRONYMS, INITIALISMS, AND ABBREVIATIONS (cont'd)

Std8110	an alternative NAAQS: 8-hr averaging time, 1 expected exceedance, 0.10 ppm ozone
Std8108	an alternative NAAQS: 8-hr averaging time, 1 expected exceedance, 0.08 ppm ozone
Std8508	an alternative NAAQS: 8-hr averaging time, 5 expected exceedances, 0.08 ppm ozone
Std8506	an alternative NAAQS: 8-hr averaging time, 5 expected exceedances, 0.06 ppm ozone

DISCLAIMER

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A PROBABILISTIC ASSESSMENT OF HEALTH RISKS ASSOCIATED WITH SHORT- AND LONG-TERM EXPOSURE TO TROPOSPHERIC OZONE

by

Ronald G. Whitfield and Mariska J.G. Absil

ABSTRACT

The work described here is part of a larger risk assessment project sponsored by the U.S. Environmental Protection Agency. Earlier efforts have: developed exposure-response relationships for acute health effects among heavily-exercising populations; characterized scientific judgment regarding the probability of chronic lung injury to children and outdoor workers due to long-term ozone exposure; developed a probabilistic National Ambient Air Quality Standards Exposure Model; and developed a general methodology for integrating probabilistic dose-response relationships and exposure estimates to calculate overall risk results. In addition, recently published animal and human experimental and observational data make it possible to characterize additional health effects for 1-hr and 8-hr exposures of moderately exercising populations to ozone. Risk results are presented for selected acute and chronic health effects in order to explain the methodology and introduce risk output formats.

1 INTRODUCTION

This report summarizes the risks of acute (short-term) and chronic (long-term) exposure to ozone. The risks are defined by probability distributions (called risk distributions) over the number of person-occurrences of specific health effects. Acute effects include decreased lung function and symptoms. Chronic effects are the formation of lesions in the human lung.

The risk distributions are obtained by combining probabilistic exposure-response relationships with exposure estimates. The exposure-response relationships are derived from a variety of sources, primarily animal and human experimental and observational data for acute effects, and the judgments of health scientists about chronic effects. Exposure estimates, which also are probabilistic, were obtained from the recently-developed probabilistic version of the National Ambient Air Quality Standards (NAAQS) Exposure Model for ozone (pNEM/O₃). pNEM/O₃ output includes results for 10 separate runs of the model to gain insights into the effects of run-to-run variations on risk output.

The motivation for this work is to (1) develop first-time risk results for some acute health endpoints (acute effects for individuals exercising at moderate levels for short and

prolonged periods of time, and chronic effects for children exposed to ozone for 1 year or longer); and (2) update previous risk results using recent exposure estimates from pNEM/O₃ that (3) reflect analysis of possible alternative NAAQS for ozone.

1.1 BACKGROUND

Ozone is a highly reactive irritant gas present in elevated amounts throughout much of the United States. The U.S. Environmental Protection Agency (EPA) estimated that in 1988 about 120 million people lived in urban areas in which the current one-hour ozone NAAQS of 0.12 parts per million (ppm) was exceeded. The current NAAQS requires that the 0.12 ppm ozone concentration not be exceeded on average on more than one day per year. This current standard for ozone is based on concern for acute respiratory effects that have been reported in many controlled human exposure studies, as well as, acute and longer-term effects reported in animal toxicology, human epidemiology, and human field studies.

As stated in the Clean Air Act, the EPA is required to set, review, and revise, as appropriate, the primary NAAQS for criteria pollutants. The primary standards, which are to be set at levels sufficient to protect public health with an adequate margin of safety, are based on scientific evidence reviewed in "criteria documents" (CDs). The CD summarizes and evaluates the human clinical, epidemiological, and animal toxicology evidence regarding physiological and adverse health effects resulting from exposure to ozone and other photochemical oxidants.

To assist in its review of the NAAQS for ozone, the Office of Air Quality Planning and Standards (OAQPS) of the EPA has entered into an interagency agreement with Argonne National Laboratory (ANL) to assess the public health risk associated with the attainment of alternative ozone NAAQS. This risk assessment is intended to characterize, as explicitly as possible, the range and implications of uncertainties in the existing scientific data base while making full use of current scientific knowledge, available animal and human experimental and observational data, and scientific expertise. This risk assessment includes effects of acute (short-term) and chronic (long-term) exposures to ozone. It combines exposure-response relationships and exposure estimates to produce overall risk estimates.

The acute risk assessment addresses effects for individuals engaged in heavy exercise (based on 1-3* hour controlled human exposure studies) and for individuals engaged in moderate exercise (based on results from 2-hour† and 6.6-hour‡ controlled human exposure studies). The chronic risk assessment is based on the judgments of health scientists.§

* Avol et al. (1984), Kulle et al. (1985), and McDonnell et al. (1983)

† Seal et al. (1993)

‡ Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991)

§ Whitfield et al. (1991) and Winkler et al. (1994)

Previous risk assessments have been performed for acute health effects of ozone (Hayes et al. [1987c]). Methods developed in that assessment (Hayes et al. [1987a]), Hayes et al. [1987b]) and an earlier assessment for lead (Wallsten and Whitfield [1986]; Whitfield and Wallsten [1989]) have provided a foundation for the current risk assessment.

1.2 RISK ASSESSMENT APPROACH

The basic risk assessment approach, illustrated in Figure 1, involves developing an exposure model and a health model. The exposure model accounts for human contact with a specific criteria pollutant. Pollutants may enter the human body through one or more pathways: inhalation, ingestion, or absorption. The contact may be described either in terms of intensity or a cumulative exposure over a specified period of time. For this assessment the exposure estimates were generated by pNEM/O₃. Exposure estimates were obtained for nine urban areas, and that portion of the population thought to be potentially most at risk to ozone exposure. The at-risk groups are identified as children and outdoor workers. This determination is based on the discussion of sensitive populations in the ozone CD (EPA [1994]).

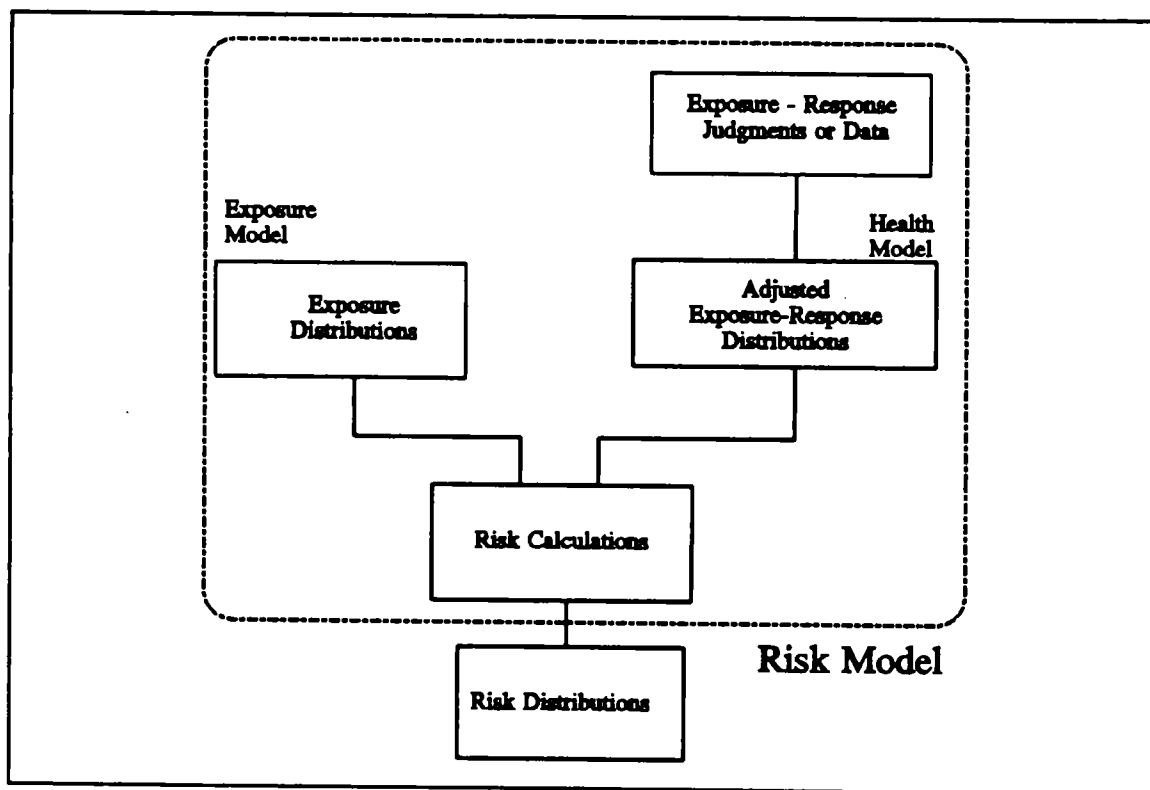


FIGURE 1.1 The Risk Model Includes an Exposure Model and a Health Model

Two types of risk estimates can be made, benchmark and headcount (McKee [1994]). Both of these use the same exposure-response relationships, but different types of air quality data and exposure estimates. Relationships between the two risk models are indicated in Figure 1.2. Benchmark risk estimates measure the risk of potential harm, or hazard, posed by elevated levels

of ozone. Headcount risk estimates measure the risk of actual harm incurred by individuals as they go about their daily lives, moving about from one place to another, and from indoors to outdoors. Only headcount risks are presented in this report. Benchmark risks will be analyzed at a later time.

In addition, there are two types of exposure measures, people and person-occurrences. The people measure counts the number of individuals who are exposed one or more times per ozone season to the exposure-indicator (ozone level and breathing rate) of interest. The person-occurrences measure begins with a count of the number of times per ozone season that a particular individual is exposed to the exposure indicator of interest, and accumulates counts over all individuals. Therefore, the person-occurrences measure confounds people and occurrences: one occurrence for 10 people is counted the same as 10 occurrences for one person. The maximum number of hourly exposure occurrences is equal to the population multiplied by the number of hours in the ozone season. Only person-occurrences measurements are included in this risk assessment.

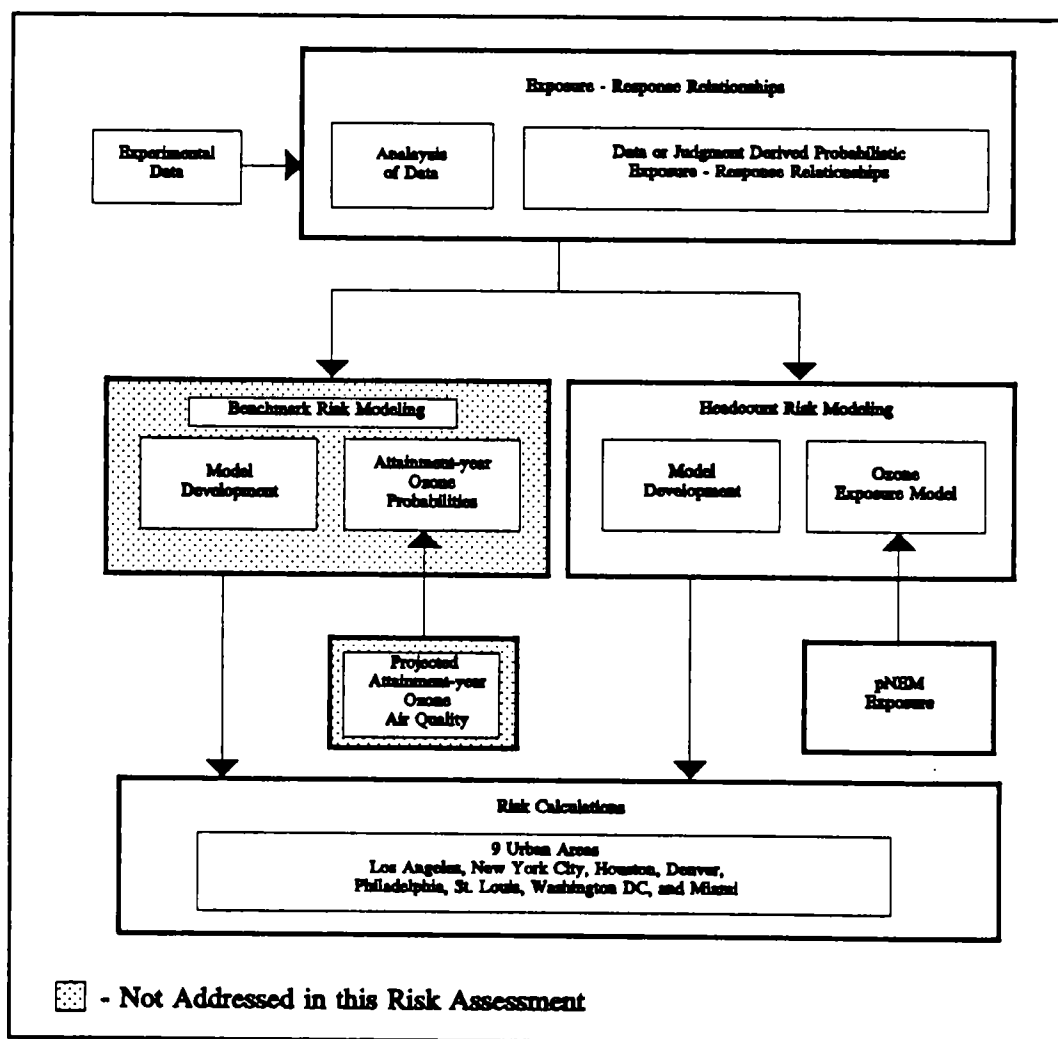


FIGURE 1.2 Relationship Between Benchmark and Headcount Risk Models

A health model accounts for human reaction to contact with a criteria pollutant. Reactions include symptoms or physiological changes (e.g., reduced pulmonary function, lower respiratory symptoms, and formation of mild/moderate lesions in the centriacinar region of the lung). A health model can be based either on data, judgment, or a combination of both. One important aspect of a health model is the "most sensitive population" - people believed to be most at risk either because they are highly reactive (e.g., children whose physiological development may be impaired by exposure to ozone) or more frequently exposed (e.g., children and outdoor workers). The Clean Air Act requires that NAAQS be set at a level that will protect the most sensitive populations with an adequate margin of safety.

Exposure-response relationships used to characterize the pulmonary function and respiratory symptom effects of ozone exposure in this study are developed from controlled human exposure data obtained in clinical studies. Controlled human exposure studies, as contrasted with epidemiological or field studies, were thought to be most appropriate in specifying the data needed for exposure-response estimation. The 1-hour exposure-response relationships for acute health effects for heavy exercisers are based on the exposure studies performed by Avol et al. (1984), Kulle et al. (1985), and McDonnell et al. (1983). Data from the Seal et al. study (1993) are used to develop exposure-response relationships for moderate exercisers. The Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) studies are used as the basis for estimating 8-hour exposure-response relationships for moderately exercising individuals.

The exposure-response relationships used to characterize the formation of mild and moderate lesions in the centriacinar region of the lung are not based on controlled human exposure studies, but rather on judgments of health scientists (Whitfield et al. [1991]; Winkler et al. [1994]). It is frequently necessary to make inferences about a health effect in a specified population on the basis of epidemiological or clinical data on different populations under varying or different exposure conditions, or laboratory data on other species or in-vitro preparations. Statistical techniques cannot quantify this type of uncertainty because it is judgmental in nature. Uncertainty can be quantified by using appropriate procedures to encode judgmental probabilities.

1.3 REPORT ORGANIZATION

This report is organized into 6 sections. Section 2 discusses the pNEM/O₃ model, the probabilistic model that generates the exposure data. It includes a description of the pNEM/O₃ methodology and simulated data. Section 3 discusses controlled human exposure data sets and probabilistic judgments. Section 4 discusses the methodology used to develop the exposure-response relationships. Section 5 summarizes risk calculations and results are presented in Section 6. Risk estimates are shown for selected health endpoints and 6 air quality scenarios for Los Angeles. Risk results are displayed in Appendix A.

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2 EXPOSURE MODEL

Evaluating alternative NAAQS proposed for a particular pollutant involves assessing the risks to human health associated with air quality that results from each of the standards under consideration. Important factors that need to be considered in an ozone exposure assessment are: magnitude of the exposure, duration of the exposure, concentration pattern of exposure, frequency of repeated peak exposures, and ventilation state of the individual at time of exposure. Several researchers have recommended that such estimates be obtained by simulating the movements of people through zones of varying air quality so as to approximate the actual exposure patterns of people living within a defined area.

Until 1986, the NEM series of models made no attempt to model random processes within the exposure simulation. The latest version of the model, pNEM/O₃ (Johnson et al. [1993]), incorporates probabilistic elements into the original NEM methodology and uses a mass balance model to estimate indoor ozone concentrations. How the pNEM/O₃ methodology fits into the risk assessment is shown in Figure 2.1. A brief description of the pNEM/O₃ and its methodology is given in this section.

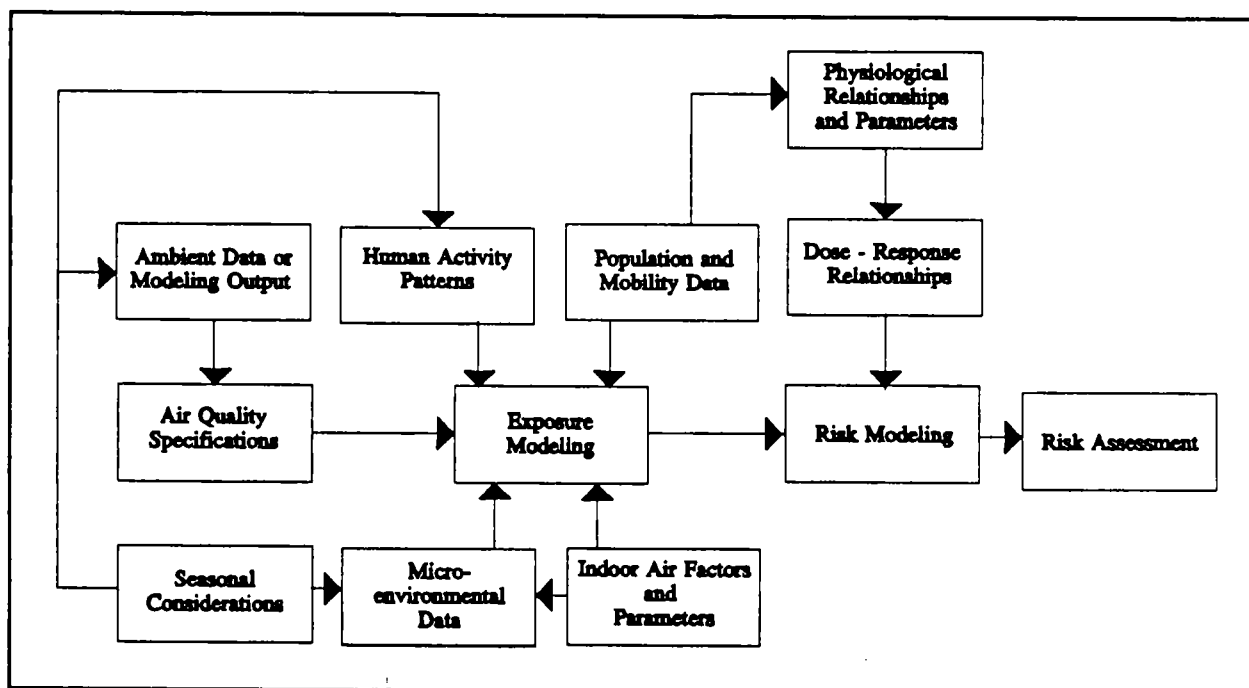


FIGURE 2.1 Major Components of the NEM Series of Exposure Models and Associated Health Risk Assessment Procedures

2.1 EXPOSURE MODELING METHODOLOGY

The pNEM/O₃ model consists of two principal parts, the cohort exposure program and the exposure extrapolation program. The cohort exposure program estimates the sequence of ozone exposures experienced by defined population groups. The exposure extrapolation program estimates the number of persons within a particular study that are represented by each cohort and then combines this information with the cohort exposure sequences to determine the distribution of exposures over a defined population of interest.

The general NEM methodology consists of five steps. The first step is to define a study area, a population of interest, appropriate subdivisions of the study area, and an exposure period. The second step is to divide the population of interest into an exhaustive set of cohorts, while the third step develops an exposure event sequence for each cohort for the exposure period. The fourth step in the procedure is to estimate the pollutant concentration, ventilation rate, and physiological indicator, if applicable, associated with each exposure event. And finally, the cohort exposures are extrapolated to the population of interest and to particular sensitive population groups. Each of these steps will be explained in detail.

2.1.1 Define the Study Area, Subdivisions of the Study Area, the Exposure Period and the Population-of-interest

The study area is defined as an aggregation of exposure districts. Each exposure district is defined as a contiguous set of geographical census units (GCU). Each GCU consists of one or more census tracts as defined by the 1980 census. No census tract is split between two or more GCUs. All GCUs assigned to a particular exposure district are located within a specified radius of a fixed ozone monitor. This radius varies from 2.1 km to 25.0 km.

The exposure period is defined as a series of months within a particular calendar year. The specified months conform to the ozone season specified for the urban area by the EPA. The exposure season is defined as the annual period when high ambient ozone levels are likely to occur. Three ozone seasons are used in the nine urban areas evaluated here: January - December, March - September, and April - October. The ozone periods for the nine cities are listed in Table 2.1.

The population of interest is typically defined as all residents of a defined study area, or the residents of the study area who belong to specific populations at risk.

TABLE 2.1 Ozone Seasons for the Nine Urban Areas

Study Area	Exposure Period
Chicago	April - October
Denver	March - September
Houston	January - December
Los Angeles	January - December
Miami	January - December
New York	April - October
Philadelphia	April - October
St. Louis	April - October
Washington DC	April - October

2.1.2 Divide the Population-of-Interest Into an Exhaustive Set of Cohorts

The population of interest is divided into a set of cohorts such that each person is assigned to only one cohort. Each cohort is assumed to contain persons with identical exposures during the specified exposure period. Cohort exposure is typically assumed to be a function of 1) demographic group, 2) location of residence, and 3) location of work place. Specifying the home and work district of each cohort provides a means of linking cohort exposure to ambient pollutant concentrations. Specifying the demographic group provides a means of linking cohort exposure to activity patterns that vary with age, work status, and other demographic variables.

The exposure of each cohort is determined by an exposure event sequence (EES) specific to the cohort. Each EES consists of a series of events with durations from 1 to 60 minutes. To determine average exposures for specific clock hours, exposure events are defined such that no event falls within more than one clock hour. Each exposure event assigns the cohort to a particular combination of geographic area and microenvironment. Each event also provides an indication of respiration rate. The respiration rates are classified as sleeping, slow, medium, and fast.

2.1.3 Develop an Exposure Event Sequence for Each Cohort for the Exposure Period

EESs are determined by assembling activity diary records relating to individual 24-hour periods into a series of records spanning the ozone season of the associated study area. Because each subject of a typical activity diary study provides data for 1-3 days, the construction of a multi-month EES requires either the repetition of data from one subject or the use of data from multiple subjects. The latter approach is used in pNEM/O₃ analyses to better represent the variability of exposure that is expected to occur among persons included in each cohort. The activity diary data used in pNEM/O₃ were obtained from the Cincinnati Activity Diary Study (Johnson [1987]). During the study, over 900 subjects completed three-day activity diaries and

detailed background questionnaires. A new diary page was completed whenever the location or activity was changed.

A distinct EES is developed for each cohort. The exposure event within an EES is defined by the district, the microenvironment, and the breathing rate associated with the human activity being undertaken by the sampled individual.

The district is defined as being either the home or work district associated with the cohort, and the seven microenvironments are:

- 1) indoors-residence with a central air conditioning system
- 2) indoors-residence with window air conditioning units
- 3) indoors-residence with no air conditioning system
- 4) indoors-nonresidential locations
- 5) outdoors near a road
- 6) outdoors — other locations
- 7) in-vehicle.

2.1.4 Estimate the Pollutant Concentration and Ventilation Rate Associated With Each Exposure Event

The year-long sequence of hourly average ozone values for indoor and in-vehicle microenvironments is generated by a mass balance algorithm. This algorithm estimates the hourly average indoor ozone concentrations during hour h as a function of: indoor ozone concentration at the end of the preceding hour, the outdoor ozone concentration outdoors during hour h , air exchange rate during hour h , and an ozone decay factor. Values for the air exchange rate and the ozone decay factor are sampled from an appropriate distribution on a daily basis. Air exchange rate is permitted to change hourly in the three residential microenvironments depending on whether windows are assigned a status of open or closed. This assignment is determined through the use of a probabilistic model in which the status during each clock hour is assumed to be a function of air conditioning system temperature range and window status during the previous clock hour. In the pNEM/O₃ simulation, the ozone concentration in a particular microenvironment during a particular clock hour is assumed to be constant. For indoor and in-vehicle microenvironments, this value is determined by using a mass balance model to calculate average ozone concentration for the clock hour under the following conditions:

- 1) there are no indoor sources of ozone,
- 2) the indoor ozone concentration at the end of the preceding hour is known,
- 3) the outdoor ozone concentration during the clock hour is constant and known,
- 4) the air exchange rate during the clock hour is constant at a specified value, and
- 5) ozone decays at a rate that is proportional to the indoor ozone concentration.

The pNEM/O₃ mass balance model requires representative ambient air quality data for each exposure district in the form of a time series containing one value for each hour in the

specified ozone season. From 3 to 15 monitoring sites are selected to represent the geographic variation of ozone levels in each of 9 study areas. The number of monitors chosen in an area depends upon a data completeness criterion for each monitor and whether or not home-to-work data exist for a district.

All monitors reporting valid data (i.e., are 75% complete) in an urban area are used to evaluate ozone air quality. In no case is an area with fewer than 3 valid stations included because no ozone concentration surface can be computed from only two monitors. If an area has numerous monitors, the total number used is capped at 16 because of limitations on computational resources. This occurs only in the Los Angeles urban area, where 30 possible monitors are pared down to 16. This paring is accomplished by removing one of nearby pairs of monitors that has similar ozone air quality distributions. Otherwise, all monitors in an area are used.

After the number of monitors is chosen, the districts must be decided upon. Districts must be non-overlapping areas focused on a monitor. In addition, home-to-work trip information must be available for a district to be included in a pNEM study area. This information is not always available and the district is removed from further analysis when this occurs. This restriction results in the exclusion of low density rural areas from pNEM exposure assessments.

2.1.5 Extrapolate the Cohort Exposures to the Population-of Interest and to Individual Sensitive Groups

The fifth and final step is to extrapolate the cohort exposures to the population-of-interest and to individual sensitive groups. The cohort-specific exposure estimates are extrapolated to the general population of each study area by estimating the population size of each cohort.

Cohort populations are estimated by the following three step procedure:

- 1) The number of persons associated with each demographic group is estimated by census tract;
- 2) The fraction of homes falling into each of the three air conditioning categories is estimated by census tract;
- 3) The demographic group populations are multiplied by the air conditioning fractions to provide an estimate of the number of persons in each combination of demographic group and air conditioning category; This results in the cohort population estimates.

2.2 EXPOSURE ESTIMATES USED IN THE RISK ASSESSMENT

pNEM/O₃ estimates were generated for the nine cities listed in Table 2.1 for the total population, children, and outdoor workers. For this risk assessment, the total population and children estimates were used for the acute and chronic effects, respectively.

pNEM/O₃ output for the ozone concentrations given in Table 2.2 included output for ten runs. Although pNEM/O₃ generates exposure distributions for both people and person-occurrences, only person-occurrences results were used in this risk assessment. The particular ozone concentrations of interest for calculating exposure-response relationships are listed in Table 2.3. These concentrations are approximately the midpoints of the intervals listed in Table 2.2. Note that 0.040 ppm for acute endpoints and 0.025 ppm for chronic endpoints are considered to be background ozone levels.

Exposure-response probabilities for each run are computed by dividing the number of person-occurrences at each ozone concentration by the total number of person-occurrences in a run. For example, using the data in Table 2.4 (which is for as-is air quality, Los Angeles, the total population, 1-hour exposures, pNEM/O₃ run number 1), the total number of person-occurrences for this particular run is 94,105,616. At 0.051 ppm there are 6,913,499 person-occurrences. Dividing this value by the total (94,105,616) results in a value of 0.073465. The same computations are performed for the remaining ozone concentrations. Note that the sum of the calculated probabilities does not equal one because the occurrence measurements for background are not included. The probabilities for this example are presented in Table 2.4.

2.3 ALTERNATIVE AIR QUALITY SCENARIOS INCLUDED IN THE ANALYSIS

pNEM/O₃ results are available for 6 alternative air quality scenarios selected by OAQPS for analysis. The first scenario represents as-is air quality. The other 5 scenarios represent ozone air quality when an alternative NAAQS is just attained. They differ with respect to averaging time (1 or 8 hours), the number of expected exceedances that are allowed (1 or 5), and the allowed ozone limit (0.06, 0.08, 0.10, or 0.12 ppm). For easy reference, these scenarios are denoted ScnASIS, Std1112, Std8110, Std8108, Std8508, and Std8506. Explicit definitions of the 6 scenarios are presented in Table 2.5.

TABLE 2.2 Ozone Concentration Intervals (ppm) for which pNEM Data has been Generated

Acute, 1-hour	Acute, 8-hour	Seasonal
0.000	0.000	0.000
0.001 - 0.020	0.001 - 0.020	0.011 - 0.020
0.021 - 0.040	0.021 - 0.040	0.021 - 0.025
0.041 - 0.060	0.041 - 0.060	0.026 - 0.030
0.061 - 0.080	0.061 - 0.070	0.031 - 0.035
0.081 - 0.100	0.071 - 0.080	0.036 - 0.040
0.101 - 0.120	0.081 - 0.090	0.041 - 0.045
0.121 - 0.140	0.091 - 0.100	0.046 - 0.050
0.141 - 0.160	0.101 - 0.110	0.051 - 0.055
0.161 - 0.180	0.111 - 0.120	0.056 - 0.060
0.181 - 0.200	0.121 - 0.130	0.061 - 0.065
0.201 - 0.220	0.131 - 0.140	0.066 - 0.070
0.221 - 0.240	0.141 - 0.150	0.071 +
0.241 - 0.260	0.151 - 0.160	
0.261 - 0.280	0.161 - 0.170	
0.281 - 0.300	0.171 - 0.180	
0.301 - 0.320	0.181 - 0.190	
0.321 - 0.340	0.191 - 0.200	
0.341 - 0.360	0.201 +	
0.361 - 0.380		
0.381 - 0.400		
0.401 +		

TABLE 2.3 Ozone Concentrations (ppm) at which Responses Rates Need to be Estimated^a

Acute, 1-hour	Acute, 8 hours	Seasonal
0.040	0.040	0.025
0.051	0.051	0.029
0.071	0.066	0.034
0.091	0.076	0.038
0.111	0.086	0.043
0.131	0.096	0.049
0.151	0.106	0.054
0.171	0.116	0.058
0.191	0.126	0.064
0.211	0.136	0.068
0.231	0.146	-
0.251	0.156	-
0.271	0.166	-
0.291	0.176	-
0.311	0.186	-
0.331	0.196	-
0.351	-	-
0.371	-	-
0.391	-	-

^aThese concentrations are approximately the midpoints of the intervals listed in Table 2.2

TABLE 2.4 Calculating Exposure Probabilities for pNEM Person-Occurrences Estimates

Ozone Concentrations (ppm) for Acute Data (1-hour)	Person-Occurrences ^a	Probabilities
0.000	7,564,509	(not required) ^b
0.011	59,187,424	(not required) ^b
0.031	13,932,709	(not required) ^b
0.051	6,913,499	0.073465
0.071	2,855,703	0.030346
0.091	1,758,979	0.018692
0.111	754,477	0.008017
0.131	465,824	0.004950
0.151	252,464	0.002683
0.171	207,844	0.002209
0.191	129,184	0.001373
0.211	56,346	0.000599
0.231	3,133	0.000033
0.251	23,523	0.00250
0.271	0	0.00000
0.291	0	0.00000
0.311	0	0.00000
0.331	0	0.00000
0.351	0	0.00000
0.371	0	0.00000
0.391	0	0.00000

^aTotal person-occurrences is 94,105,616

^bCalculations were not made for these concentrations because they are below the background level (0.04 ppm)

TABLE 2.5 Definitions of Six Alternative NAAQS

Designation	Averaging Time (hrs)	Expected Exceedances	Ozone Concentration (ppm)
ASIS	N/A ^a	N/A	N/A
Std1112	1	1	0.12
Std8110	8	1	0.10
Std8108	8	1	0.08
Std8508	8	5	0.08
Std8506	8	5	0.06

^aNot applicable

3 HEALTH EFFECTS DATA AND JUDGMENTS

Exposure to ozone can result in acute and chronic health effects. In this section we describe sources of information (data and judgments) for acute and chronic health effects attributable to ozone exposure. Acute health effects include changes in lung function (e.g., decreases in forced expiratory volume) and the onset of numerous symptoms (e.g., cough, pain on inspiration, chest discomfort). The information from these sources is used to develop a series of models. The models for acute effects are based on controlled human exposure studies. The criteria used to select the laboratory studies and a description of the individual studies used for the acute health effects models are discussed. Chronic health effects include the development of mild or moderate lesions in the centriacinar region of the lung. These chronic health models are based on expert judgments about lung injury attributable to long-term ozone exposure.

3.1 CRITERIA FOR SELECTING LABORATORY DATA

Controlled human exposure studies are thought to be most appropriate for developing exposure-response relationships acute health effects resulting from exposure to ozone. Controlled human exposure studies based on 1-hour, 2-hour, and 6.6-hour exposures are used to develop the health models. Criteria used to select the particular studies included:

- 1) Applicability to the population groups potentially most at risk. Studies with exposures at moderate or heavy exercise are of greatest interest because such subjects are thought to be more at risk than those at rest.
- 2) Comparability of total dose with exercise level and exercise protocol of particular interest.
- 3) Number of subjects. To limit the effects of small sample size, studies with at least 10 subjects per exposure level are desired.
- 4) Exposure concentrations. Studies with multiple concentration levels in the range of ambient levels are desired.
- 5) Individual subject data is needed to develop exposure-response relationships.

3.2 1-HOUR EXPOSURE-RESPONSE RELATIONSHIPS FOR HEAVILY EXERCISING POPULATIONS

Exposure-response relationships for the heavily exercising population are based on controlled human exposure studies performed by Avol et al. (1984), Kulle et al. (1985), and McDonnell et al. (1983). These studies provide enough information so that nine health endpoints can be defined for risk calculations: (1) decreases in forced expiratory volume in one

second (DFEV)* that are greater than or equal to 10% [DFEV $\geq$ 10%], (2) decreases in forced expiratory volume in one second that are greater than or equal to 15% [DFEV $\geq$ 15%], (3) decreases in forced expiratory volume in one second that are greater than or equal to 20% [DFEV $\geq$ 20%], (4) any cough [ACF], (5) any chest discomfort [ACH], (6) any lower respiratory symptoms [ALR], and moderate/severe respiratory symptoms [MCF, MCH, and MLR]. Not all of the studies support all of the endpoints. Table 3.1 indicates the endpoints associated with each study and Table 3.2 summarizes the characteristics of each study.

TABLE 3.1 Health Endpoints Associated with each Study

Endpoint	Avol et al. (1984)	Kulle et al. (1985)	McDonnell et al. (1983)
DFEV $\geq$ 10%	Yes	Yes	Yes
DFEV $\geq$ 15%	Yes	Yes	Yes
DFEV $\geq$ 20%	Yes	Yes	Yes
ACF	No	Yes	Yes
ACH	No	Yes	Yes
ALR	Yes	No	No
MCF	No	Yes	Yes
MCH	No	Yes	Yes
MLR	Yes	No	No

Differences in the three studies exist among the exercise protocols. The Avol study required 60 minutes of continuous exercise with no rest. The McDonnell study had 4 cycles of 15 minutes of rest and 15 minutes of exercise. And finally, the Kulle study consisted of 4 cycles of 14 minutes of treadmill exercise and 16 minutes of rest. These studies are used for 1-hour exposure under heavy exercise (≥ 30 l/min-m²). Even at the same ozone concentration levels, however, 2-hour exposures under intermittent exercise may not be equivalent to 1-hour exposures under continuous exercise. The same individuals were exposed at all concentration levels in the Avol and Kulle studies, while different subjects were exposed at each level in the McDonnell study.

Kulle and McDonnell inquired about cough and chest discomfort symptoms. Avol inquired about lower respiratory, upper respiratory, and nonrespiratory symptoms. Subjects in the Kulle and McDonnell studies ranked individual symptoms separately as either none, mild, moderate, or severe. Avol's subjects rated symptom severity as none, mild but noticeable only upon questioning, mild, moderate, severe, or incapacitating.

*Forced expiratory volume in one second is the maximum volume of air that an individual can expel from the lungs in 1 sec. Although forced expiratory volume can be measured over any length of time, only 1 sec intervals are considered in this report. The studies on which this report is based only provide forced expiratory volume measurements for 1 sec intervals.

TABLE 3.2 Summary of Studies Used in Developing 1-hour Exposure-Response Relationships for Heavily Exercising Individuals

	Avol et al. (1984)	Kulle et al. (1985)	McDonnell et al. (1983)
Number of subjects	50 bicyclists; 42 male and 8 female ^a	20 healthy males; 8 of 20 subjects exposed to 0.30 ppm ^b	135 healthy males
Exposure concentrations (ppm)	0.00, 0.08, 0.16, 0.24, and 0.32 ppm	0.00, 0.10, 0.15, 0.20, 0.25, and 0.30 ppm	0.00, 0.12, 0.18, 0.24, 0.30, and 0.40 ppm
Ventilation Rate	57 l/min	68 l/min	65 l/min
Exercise Pattern	continuous (10 minute warm-up, 60 minutes of continuous exercise, 10 minute cooldown and measurement)	intermittent (4 cycles of 14 minutes exercise alternated with 16 minutes of rest)	intermittent (4 cycles of 15 minutes of exercise and 15 minutes of rest)
Exercise Duration (heavy)	60 minutes	56 minutes	60 minutes
Exposure duration	1.33 hours	2 hours	2.5 hours ^c
Subject exposures	Exposed to all concentrations	Exposed to all concentrations	Divided about equally into 6 groups, each exposed to a single concentration

^aData were available only for 48 of the 50 subjects in the Avol et al. (1984) study.

^bData for 0.30 ppm exposures not reported in Kulle et al. (1985) were taken from Hayes et al. (1987a).

^cIncludes a final 30 minute period during which subjects rested and spirometric and symptoms measurements were made.

Because of the differences, each study is treated separately in this risk assessment. In spite of the differences, all of these studies were matched with 1-hour exposure durations. There are two related reasons for doing this. First, exercise duration for all 3 studies is about 1 hour. Second, it appears that the percentage change in FEV after 2 hours of intermittent heavy exercise is about the same as it is after 1 hour. Therefore, retaining the identity of each study for risk calculations makes it possible to investigate an additional source of uncertainty attributable to differences between the studies.

3.3 1-HOUR EXPOSURE-RESPONSE RELATIONSHIPS FOR MODERATELY EXERCISING POPULATIONS

Exposure-response relationships for moderately exercising populations are based on the laboratory study performed by Seal et al. (1993). The four health endpoints that can be derived from the laboratory data are: (1) DFEV $\geq 10\%$, (2) DFEV $\geq 15\%$, (3) DFEV $\geq 20\%$, and (4) any cough.

Unlike other studies in which only males were exposed, this study exposed white and black males and females. In total, three hundred seventy two subjects, ranging in age from 18 to 35, were exposed once for 2.33 hours to either 0.00, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm ozone. Potential subjects were excluded from the study for any of the following reasons: family histories of cardiovascular disease; personal history of chronic cardiovascular or chronic respiratory disease; an acute respiratory infection within six weeks of the study; deficiency in glucose-6-phosphate dehydrogenase; sickle-cell disease; pregnancy; use of birth control pills within two weeks of the study; use of marijuana one week before exposure; consumption of alcohol 24-hours before exposure; or smoking more than a pack per year within the five years preceding the study.

Before exposure, subjects completed baseline pulmonary function tests and symptom questionnaires. The first 2 hours of exposure included alternating 15 minute periods of rest and exercise on a treadmill. Pulmonary functions tests and questionnaires were administered again after the exposure was completed. The questionnaire included questions concerning the presence of cough, shortness of breath, pain on deep inspiration, headache, eye itching, and sweating. The last three symptoms were classified as shams. The symptoms were rated as: 1 (none), 2 (mild), 3 (moderate), or 4 (severe). The only symptom analyzed in this report is coughing. Additional symptoms (e.g., shortness of breath and pain on deep inspiration) will be analyzed later. The study is summarized in Table 3.3.

3.4 8-HOUR EXPOSURE-RESPONSE RELATIONSHIPS

The Folinsbee et al. (1988), Hortsman et al. (1990), and McDonnell et al. (1991) studies provided the laboratory data for exposure-response relationships for 6.6-hour exposures. All three studies were conducted in EPA's controlled human exposure chambers in Chapel Hill, North Carolina. The data from the three studies are combined and are treated as one study, because there are enough similarities among the studies with respect to exercise protocols, the recruitment of subjects, the ozone concentrations to which subjects were exposed, grouping of symptoms, and the rating of symptom severity. The six health endpoints developed from the combined studies to be used in the risk calculations include: (1) DFEV $\geq 10\%$, (2) DFEV $\geq 15\%$, (3) DFEV $\geq 20\%$, (4) ACF, (5) pain on deep inspiration [PDI], and (6) shortness of breath [BRT]. A summary of the three studies is given in Table 3.4.

TABLE 3.3 Summary of the Study Used to Develop 1-hour Exposure-Response Relationships for Moderately Exercising Populations

Seal (1993)	
Number of subjects	372 black and white males and females;
Exposure concentrations(ppm)	0.00, 0.12, 0.18, 0.24, 0.30, and 0.40 ppm
Ventilation Rate	25 l/min;
Exercise Pattern	intermittent (4 periods of 15 minutes exercise, 15 minutes rest)
Exercise Duration	1 hour
Exposure duration	2.33 hours ^a
Subject exposures	Approximately 60 subjects exposed at each level; each subject exposed to only one concentration level

^aIncludes a final 20 minute period during which subjects rested and spirometric and symptom measurements were made.

The 10 subjects for the Folinsbee et al. (1988) study, who were between the ages of 18 and 33, were exposed once to clean air and once to an ozone concentration of 0.12 ppm. These sessions were separated by a minimum of one week and the exposure sequence was randomized. The exercise protocol included 6 sessions of 50-minutes of exercise on a treadmill or cycle ergometer. Each session was followed by a 10-minute rest and measurement period. Each subject was given an additional 35-minutes to eat lunch after the third period. Physiologic tests were performed prior to exposure, during and after each of the six exercise periods, and at the end of the exposure. The four symptoms that subjects were asked to evaluate were cough, discomfort on deep inspiration, eye irritation, and pain/discomfort in the legs. Symptoms were rated as: 0 (none), 1 (just noticeable), 2 (mild discomfort), 3 (moderate discomfort), or 4 (severe discomfort/pain). The rating scale for evaluating cough was: 0 (none), 1 (cough during spirometry only), 2 (spontaneous single cough), 3 (spontaneous multiple cough), and 4 (repeated spontaneous multiple cough).

Twenty-two males participated in the Horstman et al., (1990) study to evaluate pulmonary responses from exposure to ozone. Candidates were not allowed to participate if they had a condition that could be made worse if exposed to ozone or exercise, or if they had an acute respiratory infection within the previous four weeks. Exposures were separated by a minimum of 1 week and the exposure sequence was randomized. With few exceptions, all subjects were exposed to all four ozone concentrations. Measurements of forced expiratory

TABLE 3.4 Summary of Studies Used to Develop 8-Hour Exposure Response Relationships

	Follinsbee et al. (1988)	Horstman et al. (1990)	McDonnell et al. (1991)
Number of subjects	10 nonsmoking males	22 nonsmoking males	38 males
Exposure concentrations(ppm)	0.00, 0.12 ppm	0.00, 0.08, 0.10, 0.12 ppm	0.00, 0.08, 0.10 ppm
Ventilation Rate	40.0 l/min	42.6 l/min	40.0 l/min
Exercise Pattern	50 minutes exercise, 10 minutes rest for each hour and 35 minute rest period after 3rd hour	50 minutes exercise, 10 minutes rest for each hour and 35 minute rest period after 3rd hour	50 minutes exercise, 10 minutes rest for each hour and 35 minute rest period after 3rd hour
Exercise Duration	5 hours	5 hours	5 hours
Exposure duration	6.6 hours	6.6 hours	6.6 hours
Subject exposures	Exposed to all concentrations;	Exposed to all concentrations; one subject experiences respiratory problems at 0.10 ppm.	28 Subjects exposed only to 0.00 and 0.08; 10 subjects exposed to 0.00, 0.08, and 0.10 ppm.

spirometry and symptoms ratings were obtained during 10 minute rest periods after each session. One of the 22 subjects did not complete all four 6.6 hour exposures; he was not exposed at 0.12 ppm because of severe respiratory symptoms at 0.10 ppm ozone (although his pulmonary function responses at 0.08 and 0.10 ozone were not markedly greater than the means of the group). In addition to the primary spirometric measurements, the subjects also rated the same four symptoms as in the Follinsbee et al. (1988) study.

Of the 38 males who participated in the McDonnell et al. (1991) study, 28 subjects were exposed twice: once to clean air and once to 0.08 ppm of ozone. The remaining 10 subjects were also exposed to 0.10 ppm ozone. Exposures were separated by at least 2 weeks. Candidates were excluded if they had ever smoked regularly, if they had a history of asthma, allergic rhinitis, cardiac disease, or acute respiratory illness within the previous four weeks. Five minutes immediately following the last exercise period, airway resistance, forced expiratory spirometry, and symptoms measurements were performed. Subjects were asked to rate cough, pain in deep inspiration, and shortness of breath. Symptom severity was rated as: 0 (none), 1 (barely noticeable), 2 (mild), 3 (moderate), or 4 (severe).

These 6.6 hour studies have been matched with 8-hour exposure estimates to perform risk calculations. It seems reasonable to do this because response seems to "level off" after several hours of exposure. Thus, it is unlikely that, even if the studies had been conducted for 8 hours, FEV decrements (especially after correction for an exercise effect) would have been appreciably different.

3.5 SEASONAL EXPOSURE-RESPONSE RELATIONSHIPS

During the last review of the ozone standard, which concluded early in 1993, the issue was raised as to whether long-term exposure to ozone at levels observed in areas such as southern California and the Northeast leads to chronic effects in the form of irreversible lung injury or lung disease. The results of animal toxicology studies discussed in Chapter 10 of the then-current ozone CD (EPA [1986]) suggest that ozone exposure at sufficiently high concentrations over a prolonged enough period may result in permanent structural changes to the lung.

To better understand the possible effects of prolonged exposure to ozone, EPA conducted a chronic risk assessment (Whitfield et al. [1991]; Winkler et al. [1994]). For this particular assessment, EPA chose mild and moderate lesions in the centriacinar region of the lung as the health endpoints. This region has been shown to be the location of the maximum ozone dose and maximum lung injury in a number of species exposed to elevated ozone concentrations. The populations of interest are children aged 6 through 18 and all adult outdoor workers in two urban areas — New York City and Los Angeles. These two groups are thought to be at greater risk for chronic effects because their members tend to be outdoors more than most individuals when ozone concentrations are at their highest, and children may be more vulnerable because their lungs are still developing.

While there are a number of newly published animal toxicology studies published since 1989, 5 of the 6 experts involved in the chronic risk assessment project agreed that there would not be any appreciable difference in their judgments about development of mild or moderate lesions in the centriacinar region of the lung if they were to give their judgments today. These same 5 experts also agreed that their judgment could be used by OAQPS to assess potential chronic lung effects associated with recent ozone levels and upon attainment of alternative 1- and 8-hour NAAQS for outdoor workers and children in the Los Angeles and New York urban areas. The sixth expert did not feel comfortable with the use of his/her judgments in the NAAQS review process. EPA does not plan to analyze alternative seasonal or chronic primary NAAQS at this time. Rather, the analysis is intended to provide some preliminary indication of the possible seasonal effects avoided (or remaining) upon attainment of alternative 1- or 8-hour NAAQS. EPA plans to consider this information as one of many factors in judging whether alternative standards provide an adequate margin of safety.

Probability encoding methods were used to develop exposure-response relationships for the formation of mild/moderate lesions in the human lung. It was necessary to perform judgmental probability encoding because adequate direct data regarding exposure-response relationships were not available. Six health scientists actively involved in research of ozone-induced pulmonary health effects provided probability judgments.

The judgments were obtained through a carefully-planned encoding and documentation process that had the following three steps:

1. Develop an encoding protocol.

A carefully developed encoding protocol was crucial to the success of the project. It ensured that the questions for the experts were always phrased identically, that specific assumptions and definitions were always the same, and that the encoding process proceeded similarly for each of the participants. Consequently, the differences in probability judgments could be attributed to true differences of opinion and not to differences in assumptions, understandings, or procedures.

In developing the encoding protocol, background material was assembled and the assessment team consulted extensively with individuals (named in the acknowledgments in Whitfield et al., 1991) having expertise in different aspects of the problem. Of particular concern were the appropriate health endpoints to consider and the best way to represent exposure conditions. However, many other points also required careful attention. Dealing with chronic rather than acute effects greatly increased the number of factors that had to be considered.

On the basis of the literature and discussions with consultants, a draft of the encoding protocol was prepared. At various points, the draft was circulated to some or all of the participating consultants. Written comments were received in some cases; meetings were held in others. In this manner, several drafts of the protocol were generated and revised.

After several revisions, the protocol was pilot-tested on an EPA staff member and an EPA contractor. Some weaknesses not previously recognized became apparent during the pilot testing, and the protocol was revised further to correct them. Consultations and discussions among members of the risk assessment team led to some final fine-tuning to create the protocol that was actually used in the encoding process.

The protocol became the guiding document of the probability encoding sessions that were conducted with the experts. It discussed many issues, including the following:

- Definitions of the health endpoints. The health endpoints of interest were mild and moderate centriacinar lesions.
- Discussion of exposure conditions. To deal with chronic effects, it was decided to consider damage in the centriacinar region of the lung over a single ozone season and also over 10 ozone seasons.
- Populations at risk. The populations considered for the encoding were all children aged 6 through 18 and all adult outdoor workers in Los Angeles and New York City.
- Factors to consider. This discussion reminded the experts of factors that may be relevant to their judgments: results reported in the literature, issues concerning extrapolation from animal studies, stages of response, time scales of effects, levels of repair, effects of varying the exposure concentrations over time (e.g., relative importance of cumulative exposure

versus peak exposure), and possible interactions of ozone with other air pollutants.

- Health significance. This discussion set the stage for an exploration of the experts' opinions about the long- and short-term health consequences of lung damage resulting from long-term ozone exposure. Important questions included how significant the centriacinar lesions are in themselves and what implications they might have for a person's future health.
- Factors to keep in mind when making probability judgments. This discussion was designed to help the experts provide probabilities that accurately represented their judgments. This objective was accomplished primarily through review of some commonly found cognitive biases and simplifying heuristics and through some suggestions on how to try to mitigate their effects. The topics covered include (1) effects related to the order in which evidence is considered or probabilities assessed, (2) the effect of memory on judgment, (3) the tendency to overestimate the reliability of information, (4) the influence of the importance of events on probability judgments, and (5) the difficulty of discriminating between levels of uncertainty.

2. Conduct encoding sessions.

Judgments were obtained during two rounds of encoding sessions. Between the two rounds of encoding sessions, all experts attended a workshop. At the workshop, first-round judgments were presented and discussed. Two or three members of the risk assessment team met privately with each expert to elicit his/her judgments. Judgments were not considered "final" until an expert "signed off" on his/her judgments that were recorded after the second round of encodings. The expert was free to change his/her judgments at any time before "signing off."

3. Review and communicate results.

The entire encoding process and results were carefully documented. Each expert received a written record of his/her judgments after each round of encoding. After the second round of encoding, the experts were asked to "sign off" on their judgments to signify that what was recorded accurately reflected their feelings and beliefs. The experts were free to change any of their judgments until they signed off. The entire process from time of receipt of the encoding protocol to time of sign off covered several months. Thus, there was ample time for the experts to give careful thought to their judgments.

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4 MODELING TECHNIQUES

The ozone risk assessment seeks to quantify the health risks for that portion of the population thought to be most sensitive to ozone exposure. The groups deemed potentially at risk to such exposures are identified by the ozone criteria document as: (1) those individuals with pre-existing respiratory disease, and (2) the general population of normal, healthy individuals, particularly those who are unusually responsive to ozone and those whose outdoor activities result in increased lung ventilation. The studies described in Section 3 are used to develop exposure-response relationships that will assess the impact that short-term exposures to ozone have on the populations identified in the criteria document. In addition, judgments of experts about the effects of long-term exposure to ozone are used to develop exposure-response relationships for chronic endpoints. The methodologies used to develop these exposure-response relationships are discussed in this section.

Three basic modeling techniques are described in this section: (1) correcting FEV decrement calculations for the effects of exercise in clean air; (2) developing probabilistic exposure-response relationships at desired exposure levels for acute health endpoints; and (3) developing exposure-response relationships at desired exposure levels for chronic health endpoints.

4.1 CORRECTING FEV DECREMENT CALCULATIONS FOR THE EFFECTS OF EXERCISE IN CLEAN AIR

Exercise in clean air may result in small increases or decreases in FEV. In principle, only the effect of ozone is of interest and the additional impact exercising in clean air has on FEV should be removed. The exposure-response relationships for changes in lung function are based on FEV measurements from the laboratory studies discussed in Section 3. The data required to compute the correction for exercise in clean air are the pre- and post-exposure FEV measurements in clean air and ozone. This correction is required on an individual subject basis. It was possible to apply this correction only to the 6.6-hr FEV data for moderate exercisers.*†

The first step in correcting the FEV decrement for the effects of exercise in clean air, is to compute the change in FEV, which is the difference between the FEV measurement prior to exposure (pre) and after exposure (post). This change is computed in clean air (i.e., 0 ppm ozone) and after exposure to ozone (i.e., $\Delta\text{FEV}_{\text{air}}$ and $\Delta\text{FEV}_{\text{ozone}}$). The average of the pre-exposure FEV measurements ($\text{AFEV}_{\text{pre, ozone}}$), including the FEV measurement at 0 ppm ozone,

*That is, for the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) studies.

†Thus, only the 8-hr exposure-response relationships for FEV endpoints are corrected for exercise and the risk results do not include any exercise effects. However, the risk distributions for the other endpoints also do not include the effects of exercise in clean air because this effect, if present, is therefore present in "intermediate" results at background, and "intermediate" results at background are subtracted to obtain the "final" risk distributions.

is then computed. The corrected decrement (DFEVC) is computed by dividing the change in FEV in clean air by the average of all pre-exposure FEV measurements and subtracting the result from the percent change in FEV from exercising in ozone. Mathematically, this is represented as:

$$\Delta FEV_{\text{ozone}} = FEV_{\text{pre,ozone}} - FEV_{\text{post,ozone}}$$

$$\Delta FEV_{\text{air}} = FEV_{\text{pre,air}} - FEV_{\text{post,air}}$$

$$AFEV_{\text{pre,ozone}} = \frac{\sum_{j=1}^N FEV_{\text{pre,ozone}}}{N}$$

$$DFEVC = \left[\frac{\Delta FEV_{\text{ozone}}}{FEV_{\text{pre,ozone}}} - \frac{\Delta FEV_{\text{air}}}{AFEV_{\text{pre,ozone}}} \right] \times 100\%$$

where:

N = Number of ozone concentrations.

The laboratory data from the McDonnell et al. (1991) study is used to illustrate the calculations. The FEV measurements for Subject 12 are given in the Table 4.1.

TABLE 4.1 FEV Data from McDonnell et al. (1991) — Subject 12

Obs	Subject	Pre	Post	Concentration (ppm)
67	12	2883	2939	0.00
68	12	2925	2712	0.08
69	12	3004	2535	0.10
70	12	2846	2349	0.12

Therefore, the decrement experienced by Subject 12 at an ozone concentration of 0.10 ppm is:

$$\Delta FEV_{\text{ozone}} = 3004 - 2535 = 469$$

$$\Delta FEV_{\text{air}} = 2883 - 2939 = -56$$

$$FEV_{\text{pre,ozone}} = \frac{(2883 + 2925 + 3004 + 2846)}{4} = 2914.5$$

$$\Delta FEVC = \left[\left(\frac{469}{3004} \right) - \left(-\frac{56}{2914.5} \right) \right] \times 100\% = 17.54\%$$

For simplicity, assume that the same pre FEV measurements occur at all ozone concentrations. As illustrated in Figure 4.1, an increase in DFEVC results when the pre-exposure FEV measurement at 0 ppm ozone is less than the post-exposure FEV measurement at 0 ppm ozone. There is a decrease in DFEVC when there is a decrease in FEV over the hours of exposure at 0 ppm ozone, as illustrated in Figure 4.2.

Some of the protocols did not include FEV measurements at both 0 ppm and non-zero ozone concentrations for individual subjects. For such studies, it is not possible to correct for the effects of exercise in clean air. In those cases, the decrement (DFEV) is simply the change in FEV over the length of exposure divided by the pre-exposure FEV measurement. Mathematically, this is expressed as:

$$DFEV = \frac{FEV_{\text{post,ozone}} - FEV_{\text{pre,ozone}}}{FEV_{\text{pre,ozone}}}$$

The exposure-response relationships for the various symptoms exhibited are based on the surveys administered during and after exposure from the laboratory studies discussed in Section 3. We did not correct symptom data for "exercise in clean air" because the symptoms are coded variables and it is not meaningful to compute the differences between pre-values and post-values. In some instances, the pre-value is greater than the post-value, and subtracting the pre-value from the post-value would result in a negative number. In this analysis we simply use the number of individuals that exhibit a symptom to estimate the fraction of the population experiencing a respiratory symptom.

4.2 DEVELOPING PROBABILITY DISTRIBUTIONS AT DESIRED EXPOSURE LEVELS FOR ACUTE ENDPOINTS

Developing exposure-response relationships for the desired exposure levels is a three step process (illustrated in Figure 4.3). The first step is to calculate the fractions of the individuals that are observed to experience a specific health endpoint at the various ozone concentrations. For example, for the 6.6-hour FEV data, 17 subjects out of 60 exposed at an ozone concentration 0.08 ppm, 13 subjects out of 32 exposed at 0.10 ppm, and 15 subjects out of 30 exposed at 0.12 ppm experienced an FEV decrement $\geq 10\%$. These fractions are

indicated in Figure 4.3. The fractions for FEV decrement are listed in Table 4.2 and the fractions for the symptom endpoints are listed in Table 4.3.

Using the observed data, the second step, as indicated in Figure 4.3, is to estimate the fractions of subjects expected to respond at the desired ozone concentrations that are listed in Table 4.4.* Regressions are performed on the data listed in Table 4.2 and Table 4.3 to estimate the mean response rate at the desired ozone concentrations. Continuing with the illustration in Figure 4.3, a regression equation fit to the points (0.08 ppm, $^{17}/_{60}$), (0.10 ppm, $^{13}/_{32}$), and (0.12 ppm, $^{15}/_{30}$) is used to estimate the fractions of individuals who are expected to experience a $\geq 10\%$ decrement in FEV (DFEVC $\geq 10\%$) at the desired ozone concentrations after 8 hours of exposure.

Various functional forms (normal, normal-on-log-odds, and lognormal) were fit to find the one that has the highest regression r^2 value. The normal-on-log-odds function generally gave the best results. Estimated parameters and regression r^2 values for the exposure-response relationships developed for each of the health endpoints are given in Table 4.5.

We used the expected fraction responding, a representative number of subjects that participated in a particular study, and the beta distribution to estimate uncertainty about the fractions of subjects who may experience a specific health effect at a particular ozone level. This is the third step in the method illustrated in Figure 4.3. For example, the expected numbers and fractions of subjects expected to respond (i.e., experience a DFEVC $\geq 10\%$) for the combined 6.6-hour studies are listed in Table 4.6. The numbers expected to respond and not respond are used as parameters of a beta distribution to calculate uncertainty about response rate at each ozone concentration. The representative number used (40 in this case) is equal or close to the average number of subjects that participated in the study. The values used for each of the acute health endpoints are listed in Table 4.7.

For the 8-hour DFEVC $\geq 10\%$ endpoint illustration, the expected numbers in Table 4.6 were used to calculate the uncertainty (a probability distribution) over the fractions (and percentages) of subjects who may experience DFEVC $\geq 10\%$ at the ozone concentrations of interest. For example, the response rate is $\leq 31.5\%$ with probability 0.95, is $\leq 10.9\%$ with probability 0.05, and is between 10.9% and 31.5% with probability 0.90, given that 8.1 out of 40 hypothetical subjects are expected to respond if exposed at 0.066 ppm of ozone, and that the beta distribution describes the uncertainty. This range is called the 90% credible interval (CI) on response rate and is a result of the third step illustrated in Figure 4.3. In combination with the median estimate, we always develop 10 central CIs. This results in a cumulative probability distribution with 21 points (fractiles) for every probabilistic exposure-response relationship.

* Note that the seasonal (chronic) background level is less than the acute background level. These levels are needed to be consistent with pNEM/O₃ exposure estimates. The first concentration listed is defined to be the background concentration, which will be used later to adjust overall risk results to account for response at background levels of ozone (i.e., to subtract the response at background).

This example corresponds to the results listed for the 0.05 and 0.95 fractiles in the 0.066 ppm column of Table 4.8, which lists all of the probability distributions needed to perform risk calculations for the DFEVC $\geq 10\%$, 8-hour health endpoint. One table like Table 4.8 was developed for every health endpoint, and each table is, in effect, a health model because it represents probabilistic exposure-response relationships for all exposure concentrations of interest.*

Probabilistic exposure-response relationships at moderate exercise developed for acute endpoints at moderate exercise supported by the Seal (1983), Horstman (1990), Folinsbee (1988), and McDonnell (1991) studies are shown in Figures 4.4-4.6. To avoid overly complicated figures, only the median, 0.05 fractile, and 0.95 fractile exposure-response relationships are shown. A total of 10 endpoints are included: 4 for the Seal study and 6 for the combined Folinsbee, Horstman, and McDonnell studies.

A special case arose when the response in clean air was significantly greater than zero. For example, as listed in Table 4.3, 17 subjects in the McDonnell 1-hour study had mild or worse chest discomfort at 0 ppm ozone, while 10 of 21 subjects had mild or worse chest discomfort at 0.12 ppm. In some cases like this, the exposure-response relationship developed without using the data at 0 ppm underestimated the response at background. To offset underestimates like this, we assumed that the results at 0 ppm would also occur at background (i.e., we included an "extra" data point in the regression step). This assumption, when needed, resulted in exposure-response relationships that better represented the data.

*None of the other tables are included in this report.

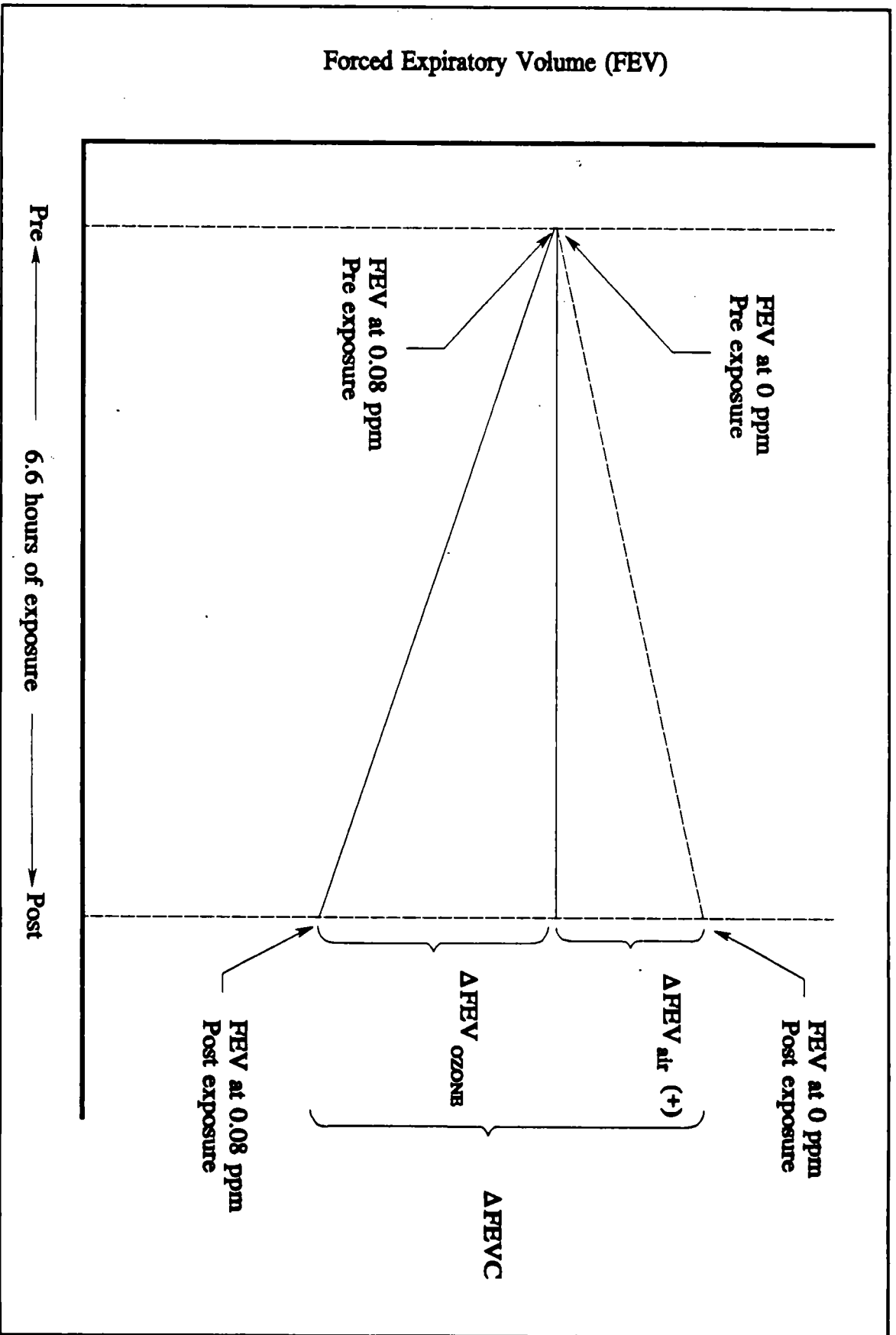
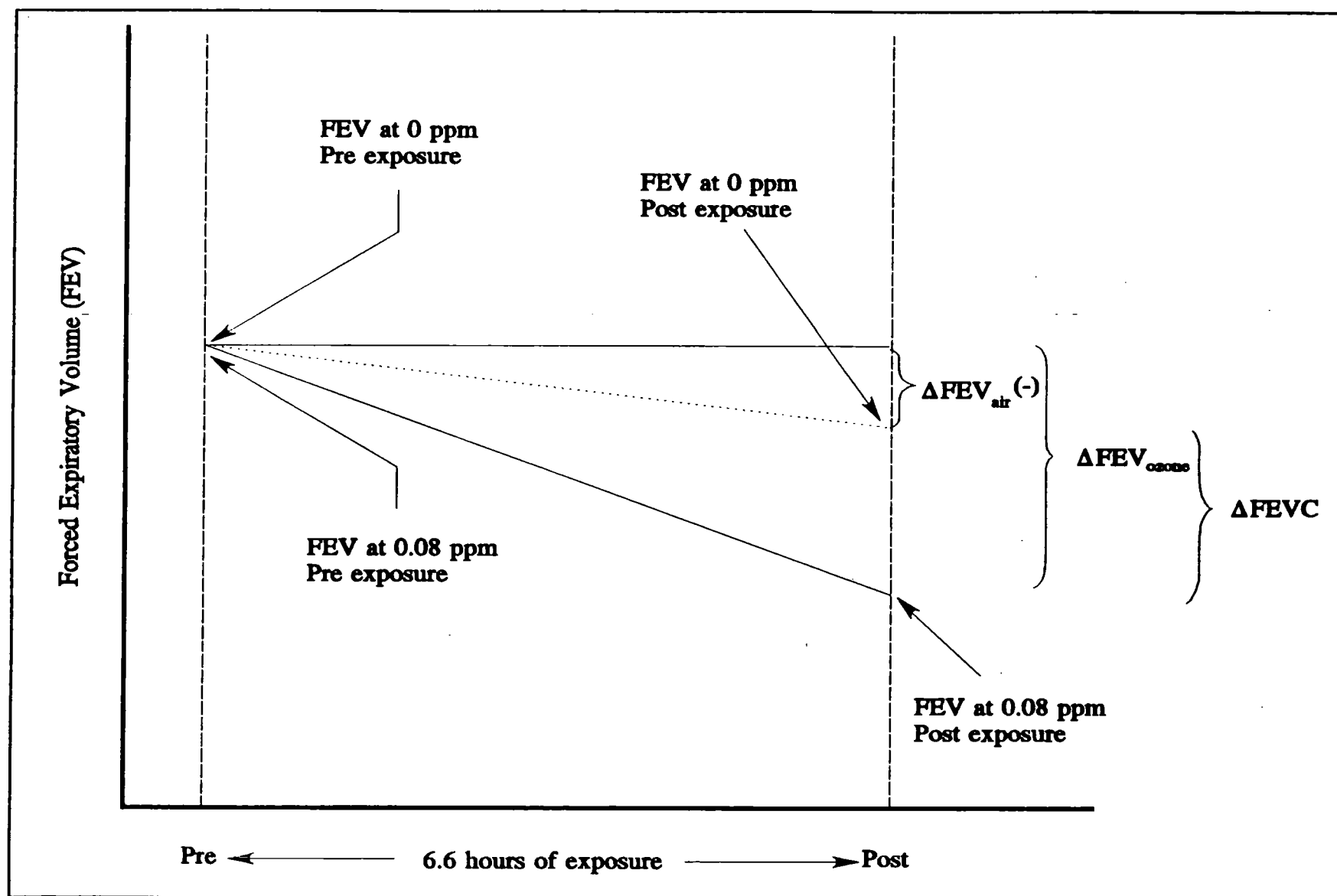


FIGURE 4.1 Effects of an Increase in Forced Expiratory Volume in Clean Air

**FIGURE 4.2** Effects of a Decrease in Forced Expiratory Volume in Clean Air

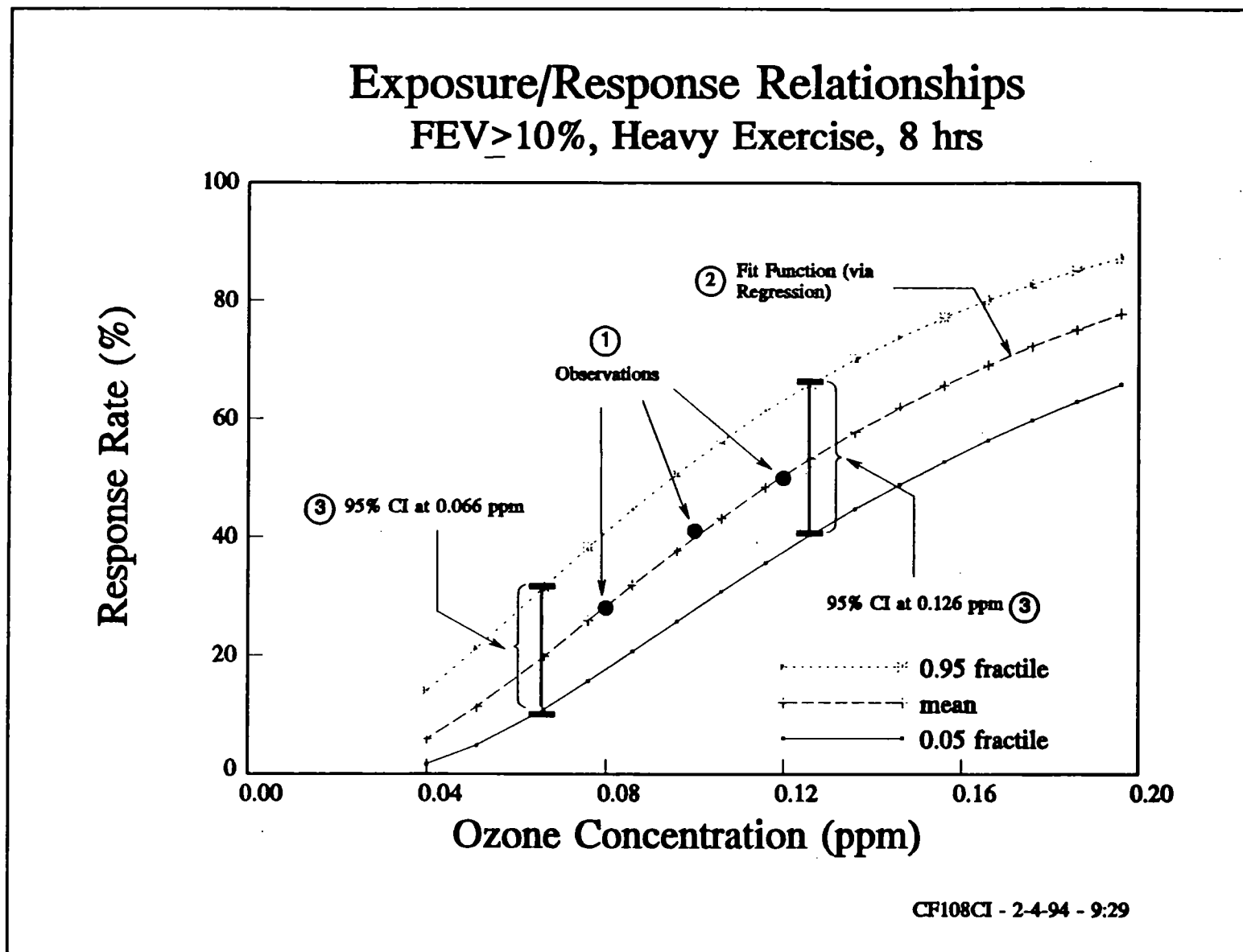


FIGURE 4.3 Method to Estimate Response Rates for Acute Effects at Desired Ozone Concentrations.

TABLE 4.4 Exposures at which Responses Need to be Estimated

Acute, 1 hour	Acute, 8 hours	Seasonal
0.040	0.040	0.025
0.051	0.051	0.028
0.071	0.066	0.033
0.091	0.076	0.038
0.111	0.086	0.043
0.131	0.096	0.048
0.151	0.106	0.053
0.171	0.116	0.058
0.191	0.126	0.063
0.211	0.136	0.068
0.231	0.146	-
0.251	0.156	-
0.271	0.166	-
0.291	0.176	-
0.311	0.186	-
0.331	0.196	-
0.351	-	-
0.371	-	-
0.391	-	-

TABLE 4.5 Estimates of Parameters and Associated r^2 Values.

Study	Length of Exposure	Health Endpoint	Normal			LogNormal			NOLO		
			a	b	r^2	a	b	r^2	a	b	r^2
Avol et al. (1984)	1.33 hr	DFEV $\geq$ 10%	0.2232	0.0828	0.97	0.2023	1.6092	0.99	-1.3408	0.5760	0.99
		DFEV $\geq$ 15%	0.2498	0.1099	0.94	0.2405	1.5912	0.97	-1.1339	0.6094	0.96
		DFEV $\geq$ 20%	0.2872	0.1176	0.98	0.2827	1.6581	1.00	-0.9233	0.6600	0.99
"	"	Any Lower Resp	0.2407	0.1191	0.98	0.2216	2.5473	0.94	-1.2310	1.0693	0.96
"	"	Mod/severe Lower Resp	0.4490	0.1025	1.00	-0.6757	0.3687	1.00	-0.1108	0.5113	1.00
Kulle et al. (1985)	2 hrs	DFEV $\geq$ 10%	0.5024	0.2757	0.97	0.7138	3.1913	0.96	0.2834	1.5223	0.96
		DFEV $\geq$ 15%	0.5247	0.2021	0.98	0.7412	2.2472	0.99	0.3569	1.0798	0.99
		DFEV $\geq$ 20%	0.4163	0.1011	1.00	0.4584	1.4456	1.00	-0.2629	0.5080	1.00
"	"	Any cough	0.2563	0.1386	0.98	0.2515	1.8920	0.98	-1.0828	0.8151	0.98
"	"	Any chest discomfort	0.2483	0.0700	0.82	0.2435	1.3989	0.78	-1.1258	0.4240	0.80
"	"	Mod/severe cough	0.2325	-0.0169	1.00	0.2346	0.9403	1.00	-1.1865	-0.0848	1.00
"	"	Mod/severe chest discomfort	0.3167	0.0608	0.89	0.3265	1.2916	0.85	-0.7426	0.3357	0.87
McDonnell et al. (1983)	2.5 hrs	DFEV $\geq$ 10%	0.2944	0.1724	0.88	0.2773	2.0549	0.94	-0.9272	0.9502	0.92
		DFEV $\geq$ 15%	0.3353	0.1444	0.75	0.3266	1.8061	0.87	-0.7085	0.7847	0.83
		DFEV $\geq$ 20%	0.4170	0.2366	0.85	0.4262	2.2241	0.89	-0.3218	1.1376	0.87
"	"	Any cough	0.0857	0.1629	0.97	0.1133	2.0208	0.90	-2.0979	0.9184	0.93
"	"	Any chest discomfort	0.1276	0.2324	0.95	0.0961	4.752	0.85	-2.1871	1.8206	0.88
"	"	Mod/severe cough	0.2652	0.1844	0.36	0.2442	2.0448	0.44	-1.0923	0.9684	0.41
"	"	Mod/severe chest discomfort	0.3456	0.2225	0.96	0.3461	2.5776	0.98	-0.6384	1.2412	0.98

TABLE 4.5 (Cont.)

Study	Length of Exposure	Health Endpoint	Normal			LogNormal			NOLO		
			a	b	r ²	a	b	r ²	a	b	r ²
Seal et al., (1993)	2.33 hrs	DFEV $\geq$ 10%	0.2690	0.1244	0.95	0.2493	1.6788	0.98	-1.0677	0.6834	0.98
		DFEV $\geq$ 15%	0.3320	0.1437	0.99	0.3291	1.8672	0.97	-0.7077	0.8129	0.99
		DFEV $\geq$ 20%	0.3941	0.1616	0.98	0.4364	2.0465	0.90	-0.3453	0.9264	0.93
"	"	Any cough	0.2502	0.1527	0.93	0.2194	2.8162	0.87	-1.2239	1.2068	0.90
Folinsbee et al., 1988; Horstman et al., 1990; McDonnell et al., 1992	6.6 hrs	DFEVC $\geq$ 10%	0.1189	0.0699	0.99	0.1194	2.0267	1.00	-1.9991	0.7838	1.00
		DFEVC $\geq$ 15%	0.1219	0.0443	0.98	0.1235	1.5761	0.95	-1.9617	0.5040	0.96
		DFEVC $\geq$ 20%	0.1796	0.0738	0.95	0.2194	2.0988	0.97	-1.3230	0.8232	0.97
"	"	Shortness of breath	0.1634	0.0659	0.96	0.2762	2.7782	1.00	-1.1142	1.0919	1.00
"	"	Any cough	0.1044	0.0494	0.98	0.1033	1.9974	1.00	-2.1603	0.7443	1.00
"	"	Pain on deep inspiration	0.0909	0.0353	0.96	0.0854	1.6289	0.99	-2.3641	0.5254	0.99

TABLE 4.6 Estimates Regarding DFEVC $\geq 10\%$ for the 8-Hour Exposure-Response Relationships

Ozone Concentration (ppm)	Estimates of FEVC% $\geq 10\%$		
	Number Expected to Respond	Number Expected to Not Respond	Fraction Expected to Respond
0.040	2.652	37.348	0.066
0.051	4.767	35.233	0.119
0.066	8.131	31.869	0.203
0.076	10.491	29.509	0.262
0.086	12.842	27.158	0.321
0.096	15.124	24.876	0.378
0.106	17.303	22.697	0.432
0.116	19.353	20.647	0.484
0.126	21.267	18.733	0.532
0.136	23.039	16.961	0.576
0.146	24.670	15.330	0.617
0.156	26.165	13.835	0.654
0.166	27.530	12.470	0.688
0.176	28.773	11.227	0.719
0.186	29.904	10.096	0.748
0.196	30.931	9.069	0.773

TABLE 4.7 Number of Subjects Used (N) in Developing Probabilistic Exposure-Response Relationships

Study	Length of Exposure	Health Endpoint	N
Avol	1.33 hrs	DFEV $\geq$ 10%	48
		DFEV $\geq$ 15%	48
		DFEV $\geq$ 20%	48
"	"	Any Lower Resp	48
		Mod/Severe Lower Resp	48
Kulle	2 hrs	DFEV $\geq$ 10%	17
		DFEV $\geq$ 15%	17
		DFEV $\geq$ 20%	16
"	"	Any cough	18
		Any Chest Discomfort	18
		Mod/Severe Cough	20
		Mod/Severe Chest discomfort	17
McDonnell	2.5 hrs	DFEV $\geq$ 10%	22
		DFEV $\geq$ 15%	22
		DFEV $\geq$ 20%	22
"	"	Any Cough	22
		Any Chest Discomfort	21
		Mod/Severe Cough	22
		Mod/Severe Chest Discomfort	22
Seal	1.33 hrs	DFEV $\geq$ 10%	62
		DFEV $\geq$ 15%	62
		DFEV $\geq$ 20%	62
"	"	Any cough	61
Folinsbee, Horstman, McDonnell	6.6 hrs	DFEVC $\geq$ 10%	40
		DFEVC $\geq$ 15%	40
		DFEVC $\geq$ 20%	40
"	"	Shortness of Breath	54
		Any cough	48
		Pain on Deep Inspiration	48

TABLE 4.8 Probability Distributions Over the Percentage of the Population Having DFEV $\geq$ 10% (8-hr exposure-response relationships)^a

Frac- tile	Ozone Concentration (ppm)															
	0.040	0.051	0.066	0.067	0.086	0.096	0.106	0.116	0.126	0.136	0.146	0.156	0.166	0.176	0.186	0.196
0.01	0.8	3.1	8.1	12.2	16.7	21.3	26.0	30.6	35.1	39.4	43.4	47.3	50.9	54.3	57.4	60.4
0.05	1.7	4.8	10.9	15.6	20.6	25.7	30.7	35.6	40.2	44.7	48.8	52.7	56.4	59.8	62.9	65.8
0.10	2.3	5.9	12.6	17.7	22.9	28.2	33.3	38.3	43.1	47.5	51.7	55.7	59.3	62.7	65.8	68.6
0.15	2.8	6.8	13.8	19.1	24.5	29.9	35.2	40.2	45.0	49.5	53.7	57.6	61.2	64.6	67.6	70.5
0.20	3.3	7.5	14.9	20.3	25.8	31.3	36.6	41.7	46.5	51.0	55.3	59.2	62.8	66.1	69.1	71.9
0.25	3.7	8.2	15.8	21.3	27.0	32.5	37.9	43.0	47.9	52.4	56.6	60.5	64.1	67.3	70.4	73.1
0.30	4.2	8.8	16.7	22.3	28.0	33.6	39.1	44.2	49.1	53.6	57.8	61.6	65.2	68.5	71.5	74.2
0.35	4.6	9.4	17.5	23.2	29.0	34.7	40.1	45.3	50.2	54.7	58.9	62.7	66.3	69.5	72.5	75.2
0.40	5.0	10.1	18.3	24.1	29.9	35.7	41.2	46.3	51.2	55.7	59.9	63.7	67.3	70.5	73.4	76.1
0.45	5.5	10.7	19.0	25.0	30.9	36.6	42.2	47.4	52.2	56.7	60.9	64.7	68.2	71.4	74.3	76.9
0.50	5.9	11.3	19.8	25.8	31.8	37.6	43.1	48.4	53.2	57.7	61.9	65.7	69.1	72.3	75.2	77.8
0.55	6.4	11.9	20.6	26.7	32.7	38.6	44.1	49.4	54.2	58.7	62.8	66.6	70.1	73.2	76.0	78.6
0.60	6.9	12.6	21.5	27.6	33.7	39.6	45.1	50.4	55.2	59.7	63.8	67.6	71.0	74.1	76.9	79.4
0.65	7.5	13.3	22.3	28.6	34.7	40.6	46.2	51.4	56.3	60.7	64.8	68.5	71.9	75.0	77.8	80.3
0.70	8.1	14.1	23.3	29.6	35.8	41.7	47.3	52.5	57.4	61.8	65.9	69.6	72.9	75.9	78.7	81.1
0.75	8.8	15.0	24.3	30.7	36.9	42.9	48.5	53.7	58.5	63.0	67.0	70.6	73.9	76.9	79.6	82.0
0.80	9.6	16.0	25.5	31.9	38.2	44.2	49.8	55.0	59.8	64.2	68.2	71.8	75.1	78.0	80.6	83.0
0.85	10.6	17.2	26.9	33.4	39.8	45.8	51.4	56.6	61.3	65.7	69.6	73.2	76.4	79.2	81.8	84.1
0.90	11.9	18.7	28.7	35.3	41.7	47.7	53.3	58.5	63.2	67.5	71.3	74.8	77.9	80.7	83.2	85.4
0.95	14.0	21.2	31.5	38.2	44.6	50.6	56.2	61.3	65.9	70.1	73.8	77.2	80.2	82.8	85.2	87.3
0.99	18.5	26.2	36.8	43.7	50.1	56.0	61.5	66.4	70.8	74.7	78.2	81.3	84.0	86.4	88.5	90.3

^aThe first column and any other column together define a cumulative probability distribution. For example, the distribution for 0.04 ppm ozone is specified by the first 2 columns: the response rate is $\leq 0.8\%$ with probability 0.01, $\leq 1.7\%$ with probability 0.25, $\leq 5.9\%$ with probability 0.5, $\leq 14\%$ with probability 0.95, and $\leq 18.5\%$ with probability 0.99.

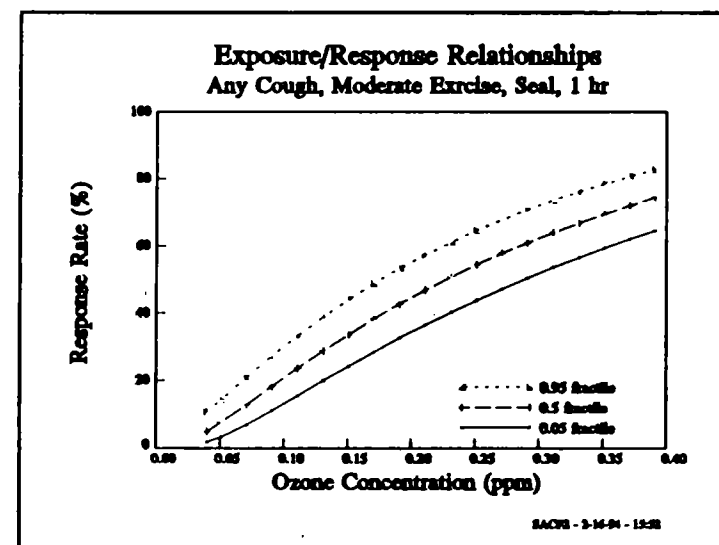
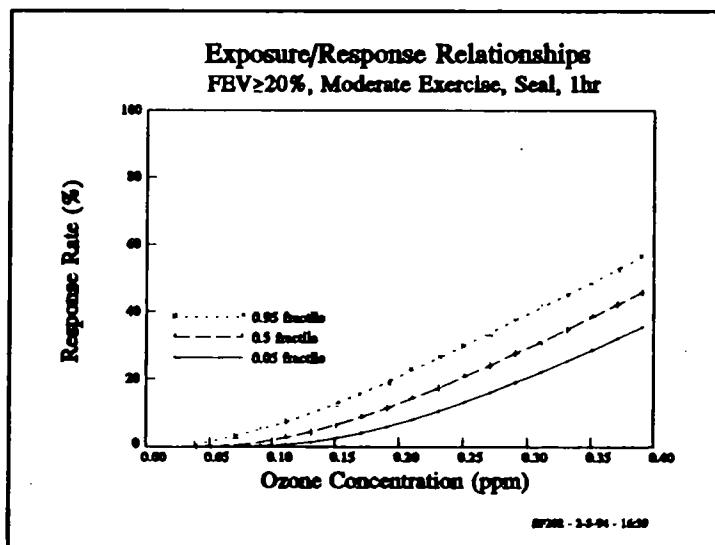
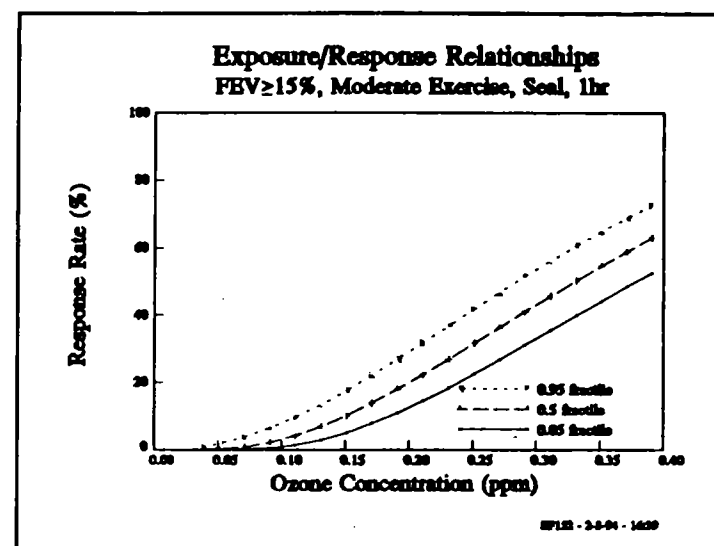
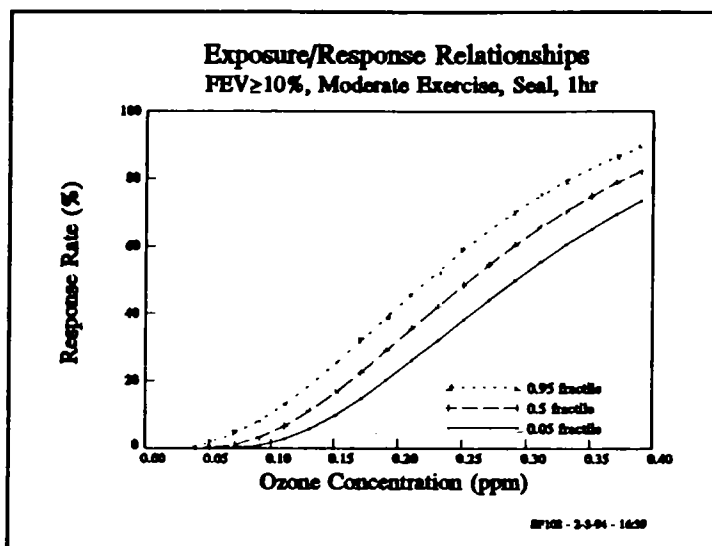


FIGURE 4.4 Medians and 90% CIs for Four 1-Hr Health Endpoints (DFEV ≥ 10%, 15%, 20%, and any cough: moderate exercise, 1 hour exposures; basis: data from Seal et al. [1993])

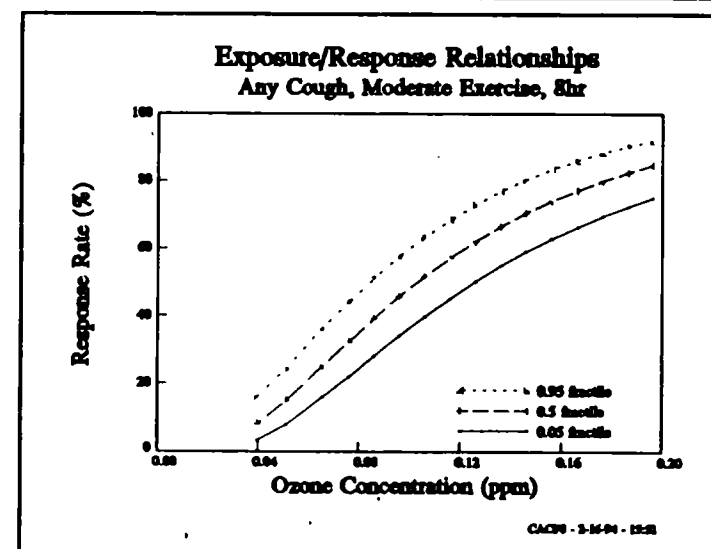
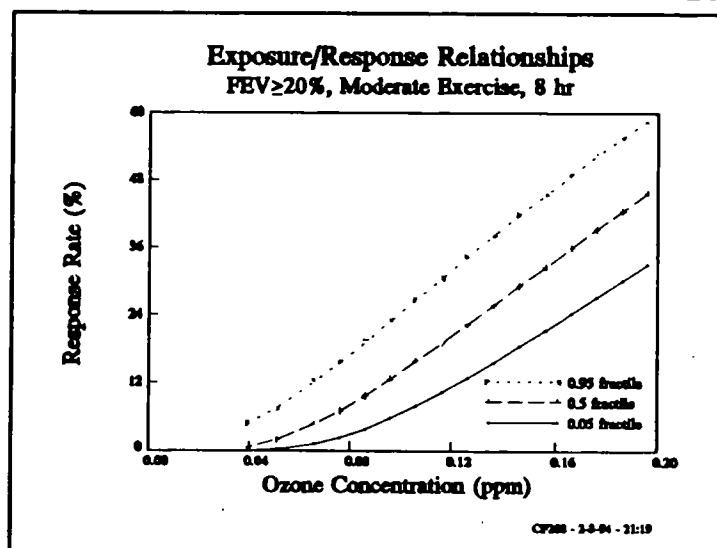
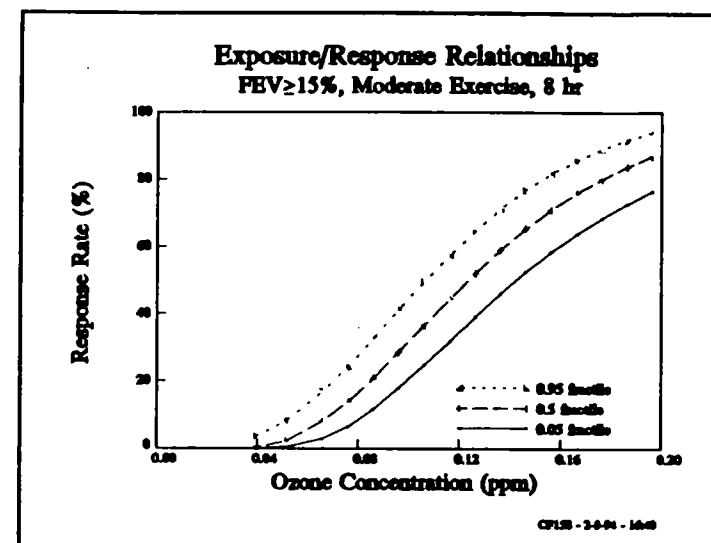
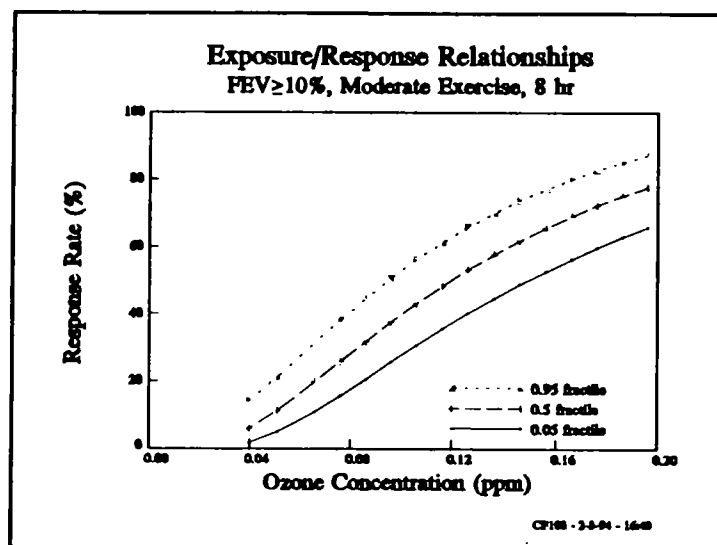


FIGURE 4.5 Medians and 90% CIs for Four 8-Hr Health Endpoints (DFEV₁ ≥ 10%, 15%, 20%, and any cough: prolonged moderate exercise; 8 hr exposures; basis: data from Folinsbee et al. [1988], Horstman et al. [1990], and McDonnell et al. [1991])

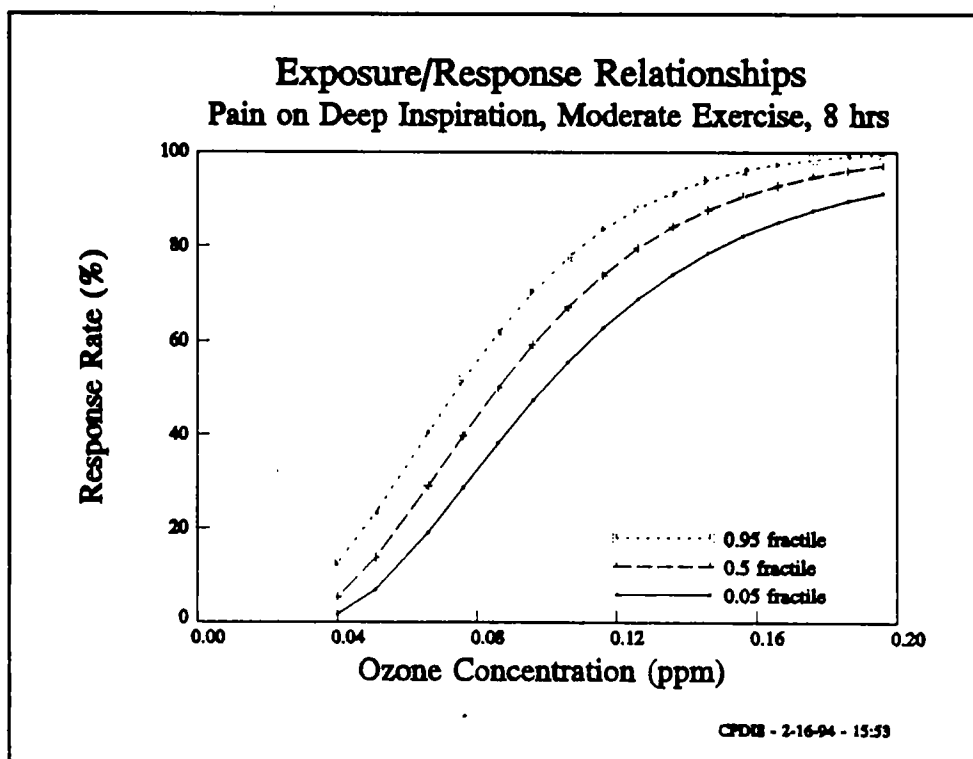
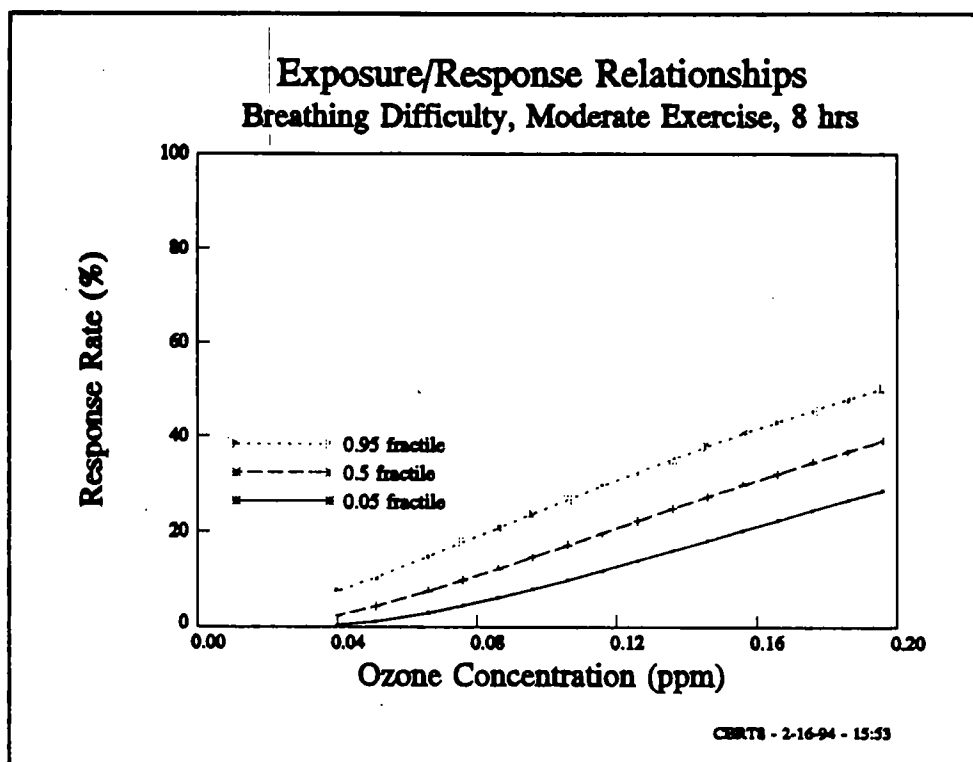


FIGURE 4.6 Medians and 90% CIs for Two 8-Hr Health Endpoints (breathing difficulty and pain on deep inspiration: moderate exercise, 8-hr exposures; basis: data from Folinsbee et al. [1988], Horstman et al. [1990], and McDonnell et al. [1991])

4.3 DEVELOPING EXPOSURE-RESPONSE RELATIONSHIPS FOR CHRONIC HEALTH ENDPOINTS

Six experts provided judgments about the probability of occurrence of ozone-induced lesions in the centriacinar region of the lung after exposure to ozone for 1 and 10 seasons. The judgments were obtained for several seasonal mean daily maximum 8-hour average ozone concentrations of personal exposure prior to any pNEM/O₃ results. At that time, it was decided to obtain judgments at ozone concentrations of 0.025, 0.050, 0.075, and 0.100 ppm. Figure 4.7 depicts the judgments of Expert A regarding the probability of formation of mild lesions among Los Angeles children after exposure to ozone for 1 season. The format reflects the way in which the judgments were obtained: conditional on the 4 ozone concentrations just mentioned.

Because these ozone concentrations do not match those for pNEM/O₃ exposure results, it was necessary to adjust the encoded judgments. The adjustment process is quite simple. The first step is to transform the judgments into a form that is more familiar to health scientists, which is shown in Figure 4.8. It shows exposure-response relationships for three fractiles (the 0.05, 0.50, and 0.95 fractiles). Also shown for completeness is the fact that Expert A (and all other experts) judged that there is no ozone-induced response at 0 ppm. The 0.05- and 0.95-fractile curves were determined by interpolation between assessed points shown in Figure 4.7, and they depict uncertainty in Expert A's judgments. If Expert A had been certain about the relationship between ozone exposure and the occurrence of ozone-induced lesions, only one curve would have been needed to completely characterize this belief. Points on the median (0.5 fractile) curve (which were available directly from the encoded judgments) are median response rates of 35%, 50%, 65%, and 75% for ozone concentrations of 0.025, 0.05, 0.075, and 0.1 ppm, respectively.

Given Figure 4.8, it is straightforward to specify probabilistic exposure-response relationships at any ozone concentration between 0 and 0.10 ppm by linear interpolation. The result of this interpolation is shown in Figure 4.9, which specifies median, 0.05-fractile, and 0.95-fractile exposure-response relationships at the pNEM/O₃ exposure concentrations. For example, the median response rate of 42.8% at 0.038 ppm was obtained by interpolation between the encoded values at 0.025 and 0.05 ppm.

A complete set of probability distributions for all pNEM/O₃ exposure concentrations is shown in Table 4.9. A set of tables like Table 4.9 has been developed for 5 of the 6 experts who provided probability judgments (Whitfield et al. [1989]; Winkler et al. [1994]).* Results only for Los Angeles and children based on one expert's judgments (Expert A) are presented in this report to illustrate the types of information that is available.

*As mentioned in Section 3.5, 5 of the 6 experts involved in the chronic risk assessment project agreed that there would not be any appreciable difference in their judgments about development of mild or moderate lesions in the centriacinar region of the lung if they were to give their judgments today. These same 5 experts also agreed that their judgment could be used by OAQPS in this assessment.

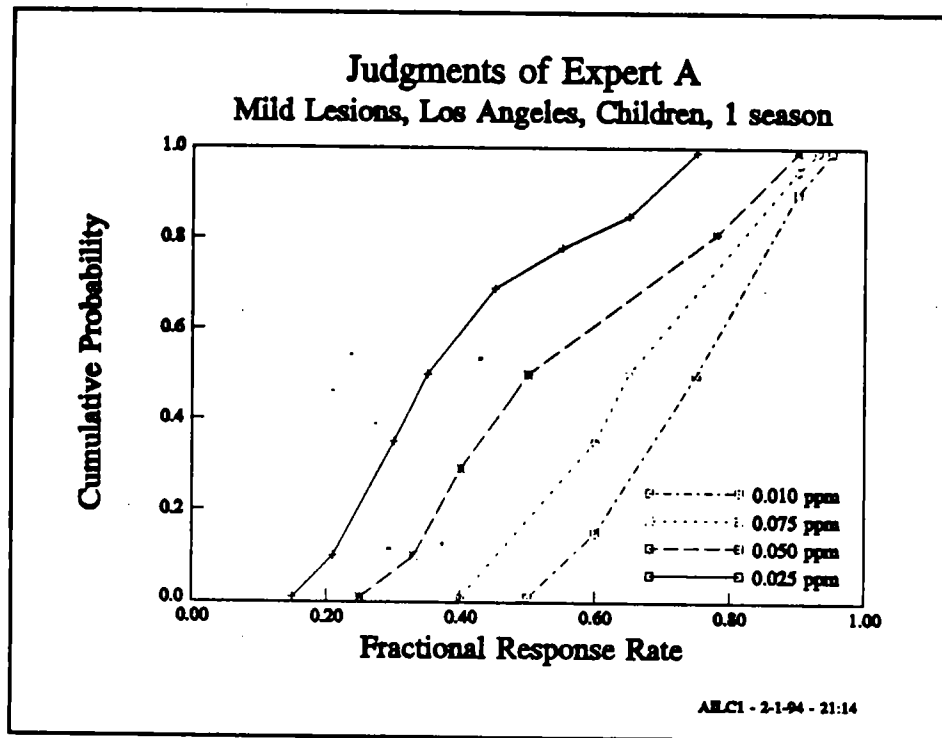


Figure 4.7 Encoded Judgments of Expert A (mild lesions, children, Los Angeles, 1 season)

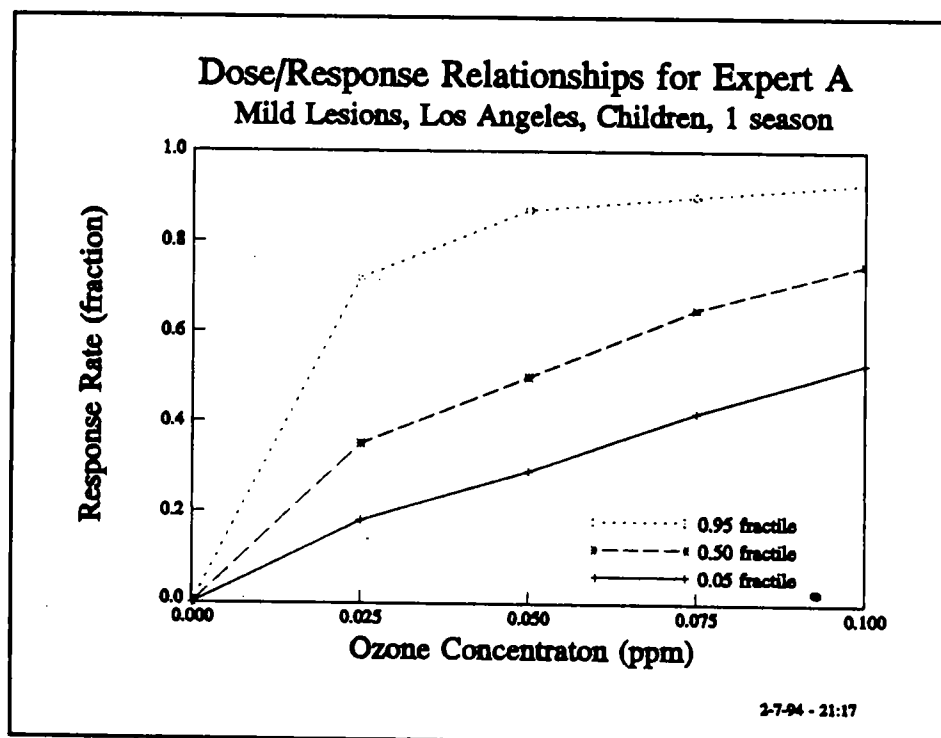


FIGURE 4.8 Judgments of Expert A in Exposure-Response Format

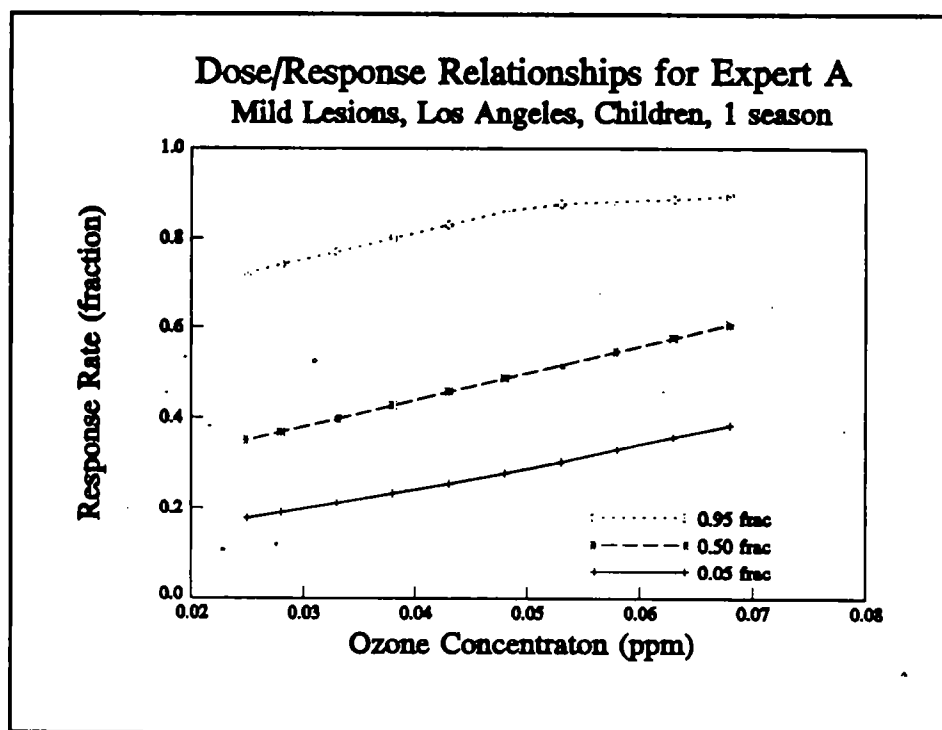


FIGURE 4.9 Judgments of Expert A Adjusted to pNEM/O₃ Exposure Concentrations

TABLE 4.9 Tabular Version of Expert A's Judgments About Percentage Response Rates at Ozone Concentrations Needed for the Risk Calculations (mild lesions, Los Angeles, children, 1 season)

Fractile	Ozone Concentration (ppm)									
	0.025	0.028	0.033	0.038	0.043	0.048	0.053	0.058	0.063	0.068
0.01	15.0	16.2	18.2	20.2	22.2	24.2	26.8	29.8	32.8	35.8
0.05	17.6	18.9	21.1	23.3	25.5	27.6	30.2	32.9	35.7	38.4
0.10	21.0	22.4	24.8	27.2	29.6	32.0	34.4	36.9	39.3	41.8
0.15	22.8	24.2	26.6	29.0	31.4	33.8	36.4	39.1	41.8	44.4
0.20	24.6	26.0	28.4	30.8	33.3	35.7	38.4	41.3	44.2	47.1
0.25	26.4	27.8	30.2	32.7	35.1	37.5	40.3	43.5	46.6	49.7
0.30	28.2	29.6	32.1	34.5	37.0	39.4	42.4	45.7	49.0	52.4
0.35	30.0	31.5	34.1	36.6	39.2	41.8	44.9	48.3	51.7	55.2
0.40	31.6	33.2	36.0	38.7	41.4	44.1	47.2	50.4	53.7	57.0
0.45	33.3	35.0	37.9	40.7	43.6	46.4	49.5	52.6	55.7	58.9
0.50	35.0	36.8	39.8	42.8	45.8	48.8	51.8	54.8	57.8	60.8
0.55	37.6	39.6	43.0	46.4	49.7	53.1	56.1	58.7	61.4	64.0
0.60	40.2	42.5	46.2	50.0	53.7	57.5	60.4	62.7	65.0	67.3
0.65	42.8	45.3	49.5	53.6	57.7	61.8	64.7	66.6	68.6	70.5
0.70	46.1	48.7	53.1	57.5	61.9	66.3	69.0	70.6	72.2	73.8
0.75	51.6	54.1	58.3	62.5	66.7	70.9	73.3	74.5	75.8	77.1
0.80	57.8	60.1	64.0	67.8	71.7	75.5	77.6	78.5	79.4	80.3
0.85	65.0	66.8	70.0	73.1	76.2	79.4	81.1	81.8	82.6	83.3
0.90	68.5	70.4	73.5	76.5	79.6	82.7	84.3	85.0	85.6	86.3
0.95	72.1	73.9	77.0	80.0	83.0	86.1	87.6	88.1	88.7	89.2
0.99	75.0	76.8	79.8	82.8	85.8	88.8	90.3	90.9	91.5	92.1

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5 RISK MODEL

Having discussed the exposure and health models, the risk calculations are conceptually simple. We will illustrate with the calculations for the $FEV \geq 10\%$ health endpoint based on the Avol et al. (1984) data (which corresponds to individuals exercising heavily and continuously for 1 hr). This endpoint applies to the total population in a city, which we will take to be Los Angeles. The calculation requires a set of exposure probabilities for specific ozone concentrations (i.e., personal exposure concentrations) that come from pNEM runs, and a set of response rates that correspond to the exposure concentrations.

To illustrate the calculations, let P_j denote the fraction of the population having personal exposures at an ozone concentration of e_j ppm in a single pNEM/ O_3 run, let $RR_k|e_j$ denote the k -fractile response for $D_{FEVC} \geq 10\%$ at ozone concentration e_j , and let $RR_k|background$ be the k -fractile response at background. In general, the risk (which is an expected fractional response rate) for the k^{th} fractile is:

$$R_k = \sum_{j=1}^N P_j \times [(RR_k|e_j) - (RR_k|background)]$$

or

$$\begin{aligned} R_k &= \sum_{j=1}^N P_j \times RR_k|e_j - \sum_{j=1}^N P_j \times RR_k|background \\ &= R_{k,1} + R_{k,2} \end{aligned}$$

where

N = the number of ozone concentrations.

Recall from Section 4 that it was possible to correct some exposure-response relationships (namely, the 8-hour FEV endpoints) for exercise in clean air. For those cases, the $RR_k|e_j$ values reflect this correction. Therefore, the intermediate result $R_{k,1}$ does not include any exercise effect, nor does $R_{k,2}$ or R_k . Furthermore, even if $R_{k,1}$ and $R_{k,2}$ do include an exercise effect, R_k does not.

Risk calculations for the 0.5-fractile (the median), for pNEM/ O_3 run number 1, and as-is air quality in Los Angeles are shown in Table 5.1. The table indicates that there are 18 ozone concentrations* above background involved in the calculations. Background ozone is considered to be ≤ 0.04 ppm. The entries in column C are the fractions of the heavily exercising population that are exposed to the corresponding ozone concentrations in column B. The entries

*The concentrations indicated in the Table 5-1 are the midpoints of intervals that are 0.02 ppm wide.

in column D are the expected fractional response rates at the corresponding ozone concentrations for the 0.5 fractile (i.e., median). The result is 0.005, or 0.5%. It happens that $RR_{0.5} | \text{background}$ is exactly zero. So, this result is unchanged after correcting for background. The final step is to multiply the fractional response rate by the number of person-occurrences to obtain, in this case, the median estimate of the number of times that individuals experience FEV decrements $\geq 10\%$. Note that an individual can experience an FEV decrement $\geq 10\%$ more than once in an ozone season. For pNEM run 1, the maximum possible number of person-occurrences is 94,105,616, so the median estimate is 485,585 person-occurrences, the measure of risk that we wish to use in this analysis.

TABLE 5.1 Calculating the Median of the Response Rate Distribution

A	B	C	D	E
Index j	e_j (ppm)	P_j	$RR_{0.5} e_j$	$RR_{0.05} = C \times D$
1	0.051	0.073465	0.00010785	0.000008
2	0.071	0.030346	0.01026799	0.000312
3	0.091	0.018692	0.04156534	0.000777
4	0.111	0.008017	0.09403153	0.000754
5	0.131	0.004950	0.16465874	0.000815
6	0.151	0.002683	0.24798385	0.000665
7	0.171	0.002209	0.33767622	0.000746
8	0.191	0.001373	0.42825932	0.000588
9	0.211	0.000599	0.51537905	0.000309
10	0.231	0.000033	0.59607661	0.000020
11	0.251	0.000250	0.66857661	0.000167
12	0.271	0.000000	0.73216012	0.000000
13	0.291	0.000000	0.78667853	0.000000
14	0.311	0.000000	0.83268019	0.000000
15	0.331	0.000000	0.87071312	0.000000
16	0.351	0.000000	0.90174723	0.000000
17	0.371	0.000000	0.92666693	0.000000
18	0.391	0.000000	0.94646038	0.000000
Column E Sum:				0.005160

To develop a probability distribution over person-occurrences that accounts for all of the conditions mentioned earlier, the above calculations are repeated for any number of fractiles. Results will usually appear "smoother" if a large number of fractiles are used. In this analysis, 21 fractiles are used to obtain the results presented in the next section.

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6 A DESCRIPTION OF RISK RESULTS

Risk results are presented in a set of figures in Appendix A. The figures describe all acute results and a sample of chronic results. These results have been "corrected for background," where background is defined as 0.04 ppm for acute exposures and 0.025 ppm for seasonal exposures. This correction, as explained in Sec. 5, involves subtracting the probability distribution over response at the background concentration from the probability distribution over response for ozone concentrations above background. As with many of our computations, this subtraction assumes perfect correlation and allows us to perform the correction by simply subtracting corresponding responses on a fractile-by-fractile basis. If, per chance, there is no response at a particular background concentration, then the "uncorrected" and "corrected" results are identical. This happened quite often in the chronic risk calculations because many of the experts judged that there would no response at concentrations as high as 0.05 ppm.*

One acute (FEV $\geq 10\%$, 1-hr exposure time, total population) and one chronic (mild lesions, children, 1 ozone season of exposure) endpoint are presented. Results are based on the Avol data and the judgments of Expert A for 6 air quality scenarios. We also compare acute results based on the Avol, Kulle, and McDonnell data. Although other results are available (e.g., for other 1-hr endpoints and other experts), the ones discussed in this section and the others presented in Appendix A are meant to be examples of the types of results that are available. Still other results are forthcoming (e.g., airway reactivity and bronchoalveolar lavage endpoints for 1-hr exposures; and chronic effects for workers, which will be made available after OAQPS provides exposure estimates for workers).

Table 6.1 is a listing of the risk results for case AF101LT1 (Avol, FEV $\geq 10\%$, 1-hr exposure, Los Angeles, total population, as-is air quality [the first of the 6 scenarios]). Ten distributions are provided — one for each of the 10 pNEM/O₃ runs that are available for 1-hr exposure times in Los Angeles and as-is air quality. The first column lists cumulative probabilities for the distributions. For example, the 0.50 cumulative probability (0.5 fractile) estimates range from 424,896 (run 9) to 562,376 (run 10) person-occurrences. The mean, standard deviation (StdDev), and total number of *possible* person-occurrences (MaxPO) are listed at the bottom of the table. For run 1, the mean is 532,484, the standard deviation is 221,075, and MaxPO is over 94 million. Note that MaxPO is based on the total number of people who reached what we have defined as a heavy level of exercise in each pNEM/O₃ run, and that this number varies from run to run. The significance (if any) of this variation is one of the issues specifically addressed in this risk assessment.

Figure 6.1 is a plot of the data in Table 6.1. It also includes the results for just attaining the current ozone standard (Std1112: 1-hr averaging time, 1 expected exceedance, 0.12 ppm). Note that the risks are much lower if the standard is met (indicated by the fact that the

*For example, the judgments of Expert B about moderate lesions among Los Angeles children after exposure for 1 ozone season (Whitfield et al. [1989]).

TABLE 6.1 Probability Distributions Over Person-Occurrences of FEV $\geq$ 10%.

Code	Cumulative Probability	Incidences of FEV $\geq$ 10% by pNEM/O ₃ Run									
		1	2	3	4	5	6	7	8	9	10
AF101LT1: Avol (heavy exercisers); forced expiratory volume $\geq$ 10%; 1-hr exposure; Los Angeles; total population; as-is air quality											
	0.01	198452	210669	176784	177397	182577	215202	169396	188993	166300	239602
	0.05	256171	271812	232942	236829	237544	277483	222398	251014	216383	306137
	0.10	294010	311479	270433	276953	273700	318125	257475	292060	249658	349147
	0.15	322986	341616	299410	308210	301474	349203	284440	323644	275437	381822
	0.20	348270	367753	324847	335816	325779	376312	308019	351296	298155	410180
	0.25	371708	391856	348529	361651	348367	401443	329905	376991	319399	436358
	0.30	394235	414916	371370	386680	370129	425603	350960	401737	339979	461431
	0.35	416446	437561	393957	411526	391636	449433	371735	426173	360419	486078
	0.40	438798	460262	416744	436675	413326	473423	392656	450788	381126	510810
	0.45	461704	483446	440154	462576	435602	498021	414110	476024	402482	536085
	0.50	485600	507553	464633	489707	458892	523693	436511	502338	424896	562376
	0.55	510999	533099	490717	518632	483702	550992	460347	530263	448855	590230
	0.60	538555	560735	519090	550075	510682	580623	486246	560476	474990	620342
	0.65	569157	591346	550690	585020	540719	613542	515064	593883	504161	653644
	0.70	604080	626195	586866	624878	575083	651121	548029	631783	537610	691472
	0.75	645253	667192	629658	671787	615702	695436	587003	676134	577217	735836
	0.80	695763	717393	682341	729169	665666	749812	634967	730067	625999	789958
	0.85	760817	781946	750435	802807	730183	819854	696951	798876	689044	859264
	0.90	849689	870025	843760	903038	818518	915546	781896	892045	775408	953451
	0.95	982163	1001236	983207	1052076	950395	1058183	908822	1030116	904348	1093328
	0.99	1180073	1197361	1191756	1275055	1147453	1271235	1098653	1236842	1096871	1302204
	Mean	532484	552747	514965	544334	506316	574307	481762	551155	472570	610654
	StdDev	221075	221685	228831	249084	217326	237771	209134	237445	210236	239341
	MaxPO	94105616	93406960	92967584	96200440	96209240	93398304	92577872	92722712	91940232	90044728

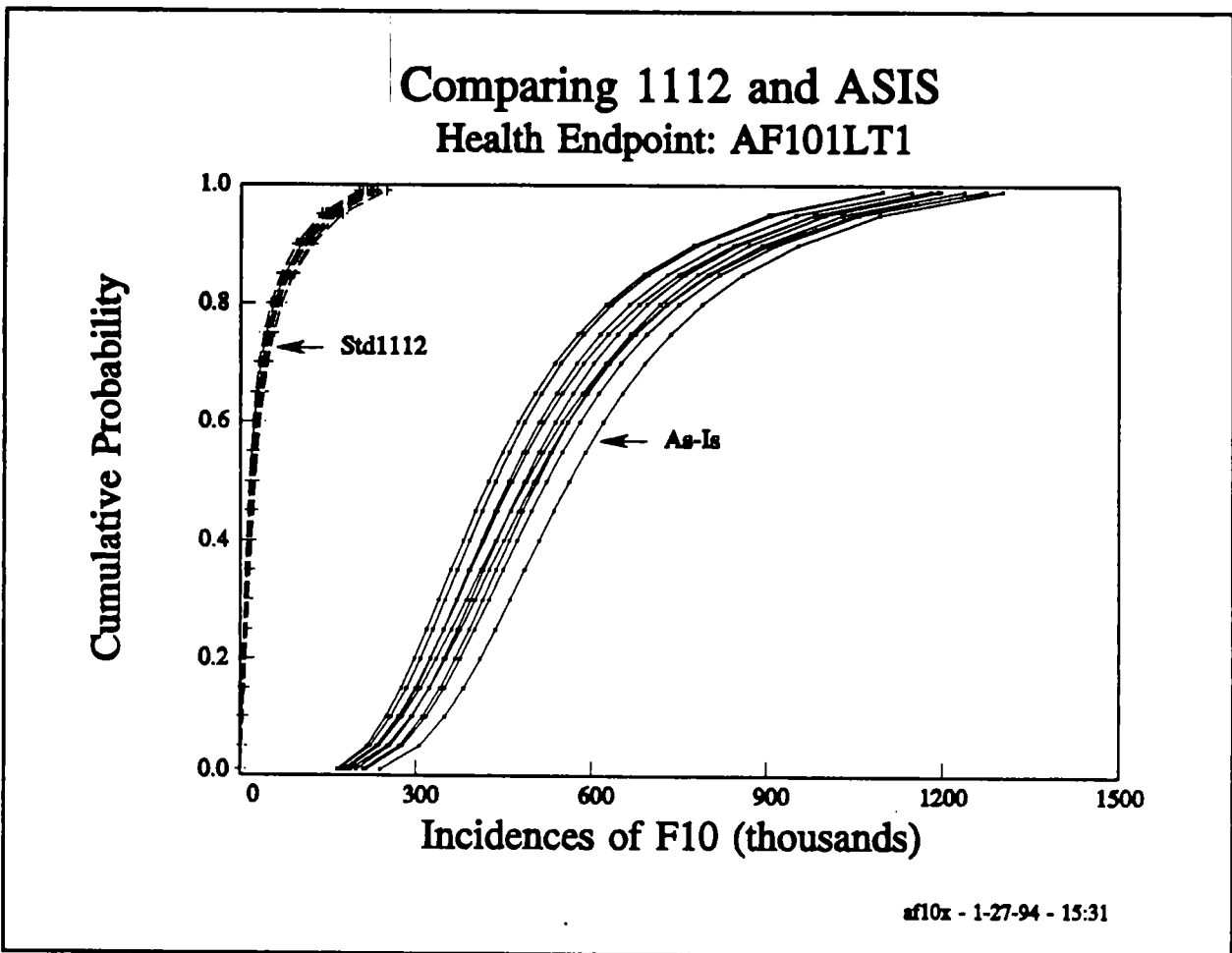


FIGURE 6.1 Risk Results for Two Air Quality Scenarios (as-is air quality and attainment of the current 1-hr standard; DFEV $\geq 10\%$, 1-hr exposures, Los Angeles, total population)

distribution is much closer to the Y-axis than the distribution for as-is air quality). Also note that the variation in results is much smaller for meeting the standard: the distributions are quite close to one another and are nearly indistinguishable, at least on the scale used in the figure. In contrast, the distributions for as-is are generally distinguishable.

On this scale, it is not helpful to plot the distributions for the other scenarios because, except for Std8110, they are even closer to the Y-axis than those for Std1112 and, if they were included, the figure would be quite messy. Figure 6.2 gives some idea of the range of results among each set of 10 distributions. There are 6 plots, one for each air quality scenario. Each plot is: "representative" of the 10 distributions for a particular scenario. Since there are only 6 plots instead of 60, it is easier to see patterns. Each of these plots is a valid cumulative

probability distribution.* To gain some insights about the effects of attaining each standard, consider Figure 6.2, which shows that meeting the current standard is “better than” meeting Std8110, and that Std8108 and Std8508 are quite similar. As expected, Std8506 results in the lowest risk.

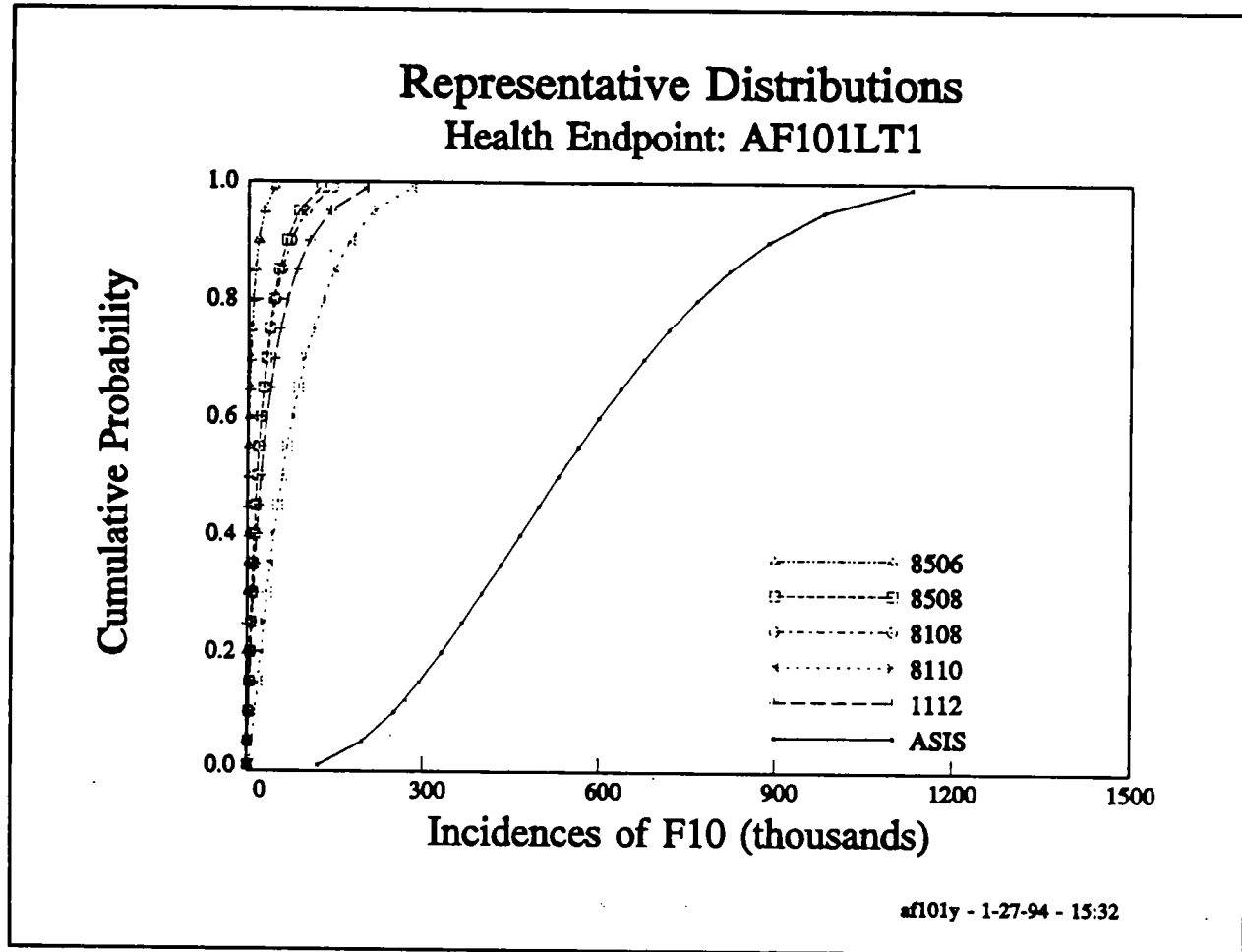


FIGURE 6.2 Representative Distributions for 6 Air Quality Scenarios (Avol, DFEV $\geq 10\%$, 1-hr exposures, Los Angeles, total population)

A final example (for an acute endpoint) of the types of comparisons that can be made is shown in Figure 6.3, which compares the representative risk distributions based on data from the Avol, Kulle, and McDonnell studies for as-is air quality. The highest risk estimates are

*The representative distribution is obtained by effectively integrating across all 10 distributions simultaneously and normalizing the result by dividing by 10. This calculation, like the risk calculations described earlier, implicitly assumes that the distributions are perfectly correlated. It may be argued that perfect correlation, while not correct, is more reasonable than perfect independence, and there is no basis for choosing any other degree of correlation between these 2 extremes.

based on the McDonnell study; but the McDonnell risk distribution intersect with the Avol risk distribution. The risk distribution based on the Kulle results lies strictly to the left of both the McDonnell and the Avol distributions.

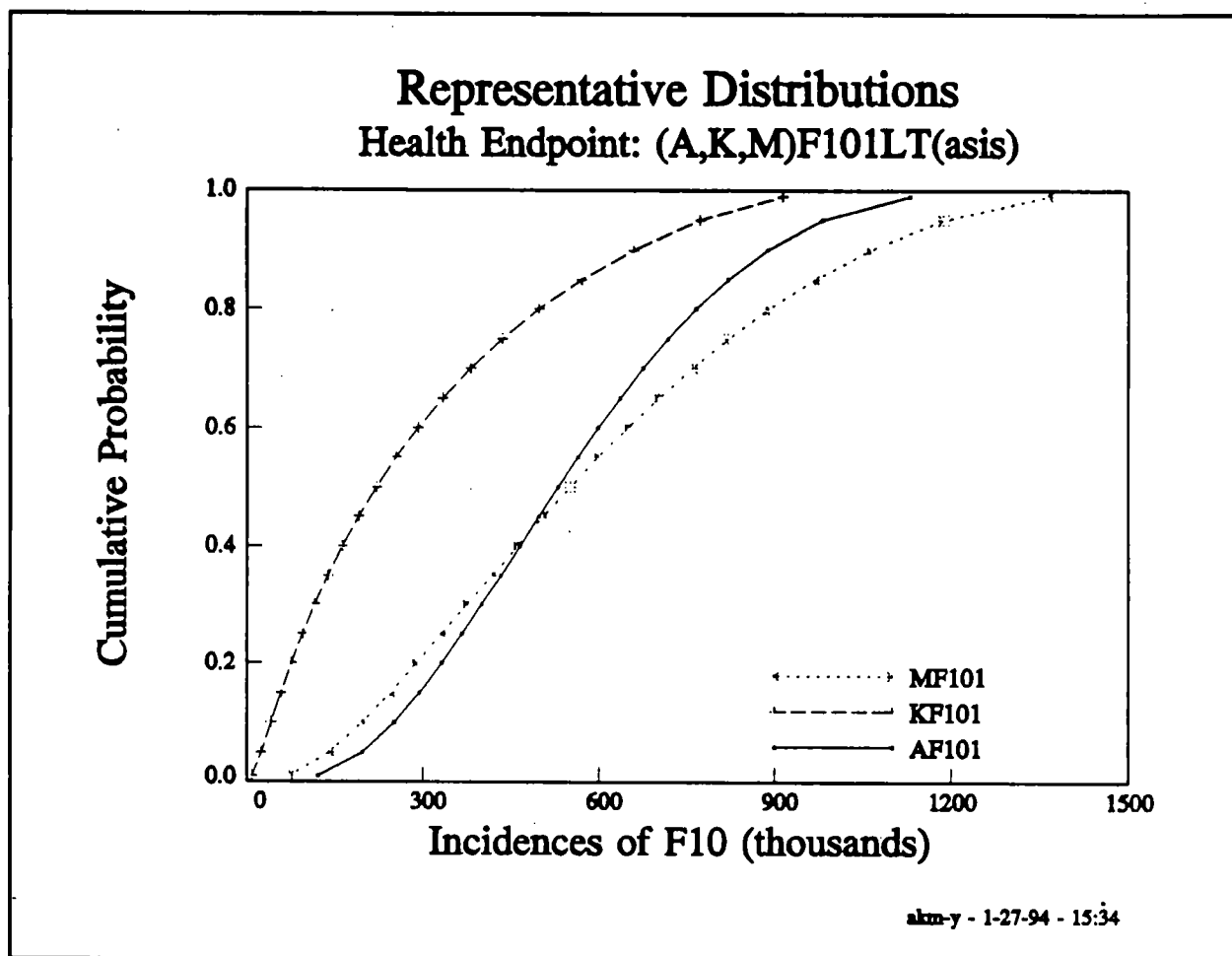


FIGURE 6.3 Comparison of FEV $\geq$ 10%, 1-Hr Exposures, As-Is Results Based on Data from Three Clinical Studies

Appendix A contains figures for all Los Angeles health endpoints associated with 1-hour exposures to ozone. They give an overview of the risk results and serve as a guide to more precise analysis that is made possible by results like those in listed in Table 6.1.

Figure 6.4 contains plots of risk distributions for the chronic endpoint AILC1 (Expert A, mild lesions, Los Angeles, children, 1 ozone season of exposure). There are two sets of 10 distributions, one set for each of two air quality scenarios — ScnASIS and Std8110. This figure is analogous to Figure 6.1 for a 1-hour endpoint. Variability in the risk distributions is partially attributable to run-to-run variations in the pNEM/O₃ exposure results.

Representative distributions for 5 air quality scenarios (results for the most stringent standard — Std8506 — coincide with the Y-axis because there is no risk of formation of mild

lesions when this standard is attained) are shown in Figure 6.5. This figure is analogous to Figure 6.2. Plots like these are shown in Appendix A for Expert A, mild and moderate lesions, Los Angeles, children, and 5 air quality scenarios.

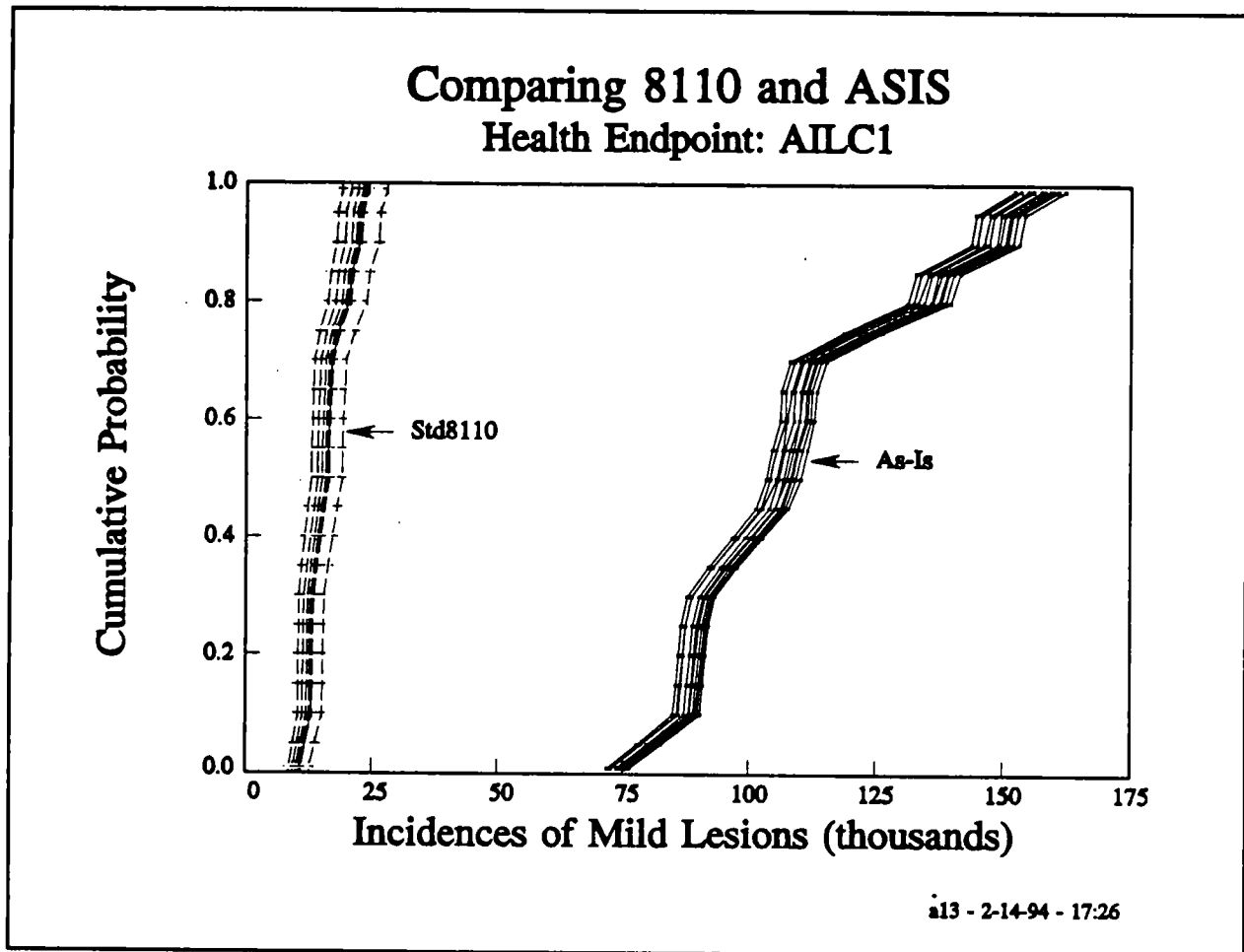


FIGURE 6.4 Risk Distributions for Mild Lesions Based on the Judgments of Expert A

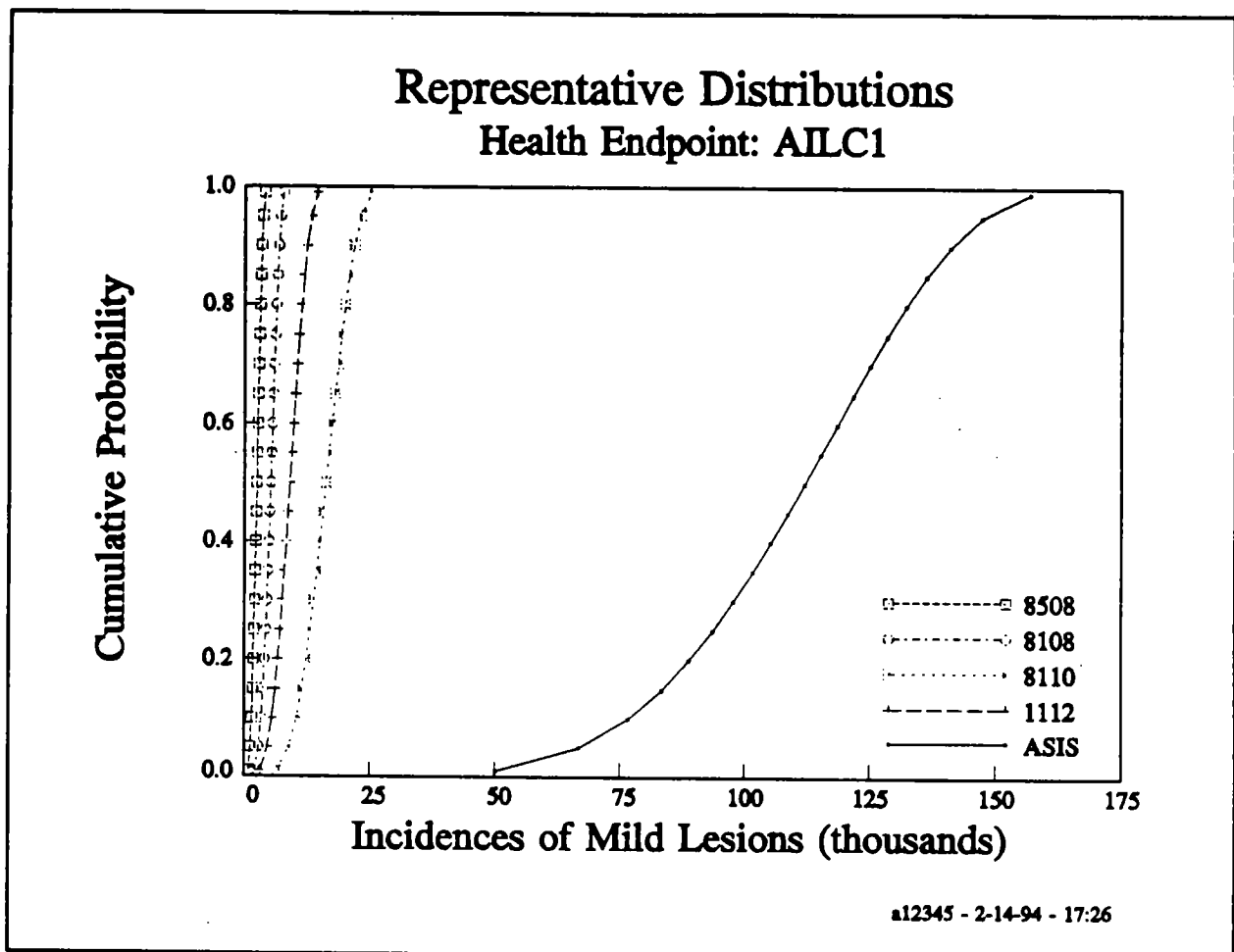


FIGURE 6.5 Representative Risk Distributions for Expert A (Note: Results for the most stringent standard — Std8506 — coincide with the Y-axis because there is no risk of formation of mild lesions when this standard is attained.)

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APPENDIX A

**RISK RESULTS FOR
SELECTED HEALTH ENDPOINTS**

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APPENDIX A

RISK RESULTS FOR SELECTED HEALTH ENDPOINTS

This appendix consists of 33 figures that contain risk distributions for selected health endpoints. Figures A.1-29 address acute endpoints (pulmonary function and symptoms, 1-hr exposures at heavy exercise, Los Angeles, total population) and Figures A.30-33 address chronic endpoints (mild and moderate lesions, Los Angeles, children, 1 and 10 ozone seasons of exposure). The figures are grouped according to health endpoint: 1-hr endpoints are first, 8-hr endpoints are next, and chronic endpoints are last.

In most cases, there is more than one figure for each acute endpoint — one figure for each study that supports an endpoint. For example, four studies* provide data on each 1-hr pulmonary function endpoint ($FEV \geq 10\%$, $\geq 15\%$, and $\geq 20\%$). Figures A.1-4 contain risk distributions for $FEV \geq 10\%$ based on data from the Avol, Kulle, McDonnell, and Seal studies, respectively. The next 4 figures are for $FEV \geq 15\%$, and the next 4 are for $FEV \geq 20\%$.

Each plot in each figure is representative† of 10 distributions, which result from available exposure distributions from pNEM/O₃ runs. It was necessary to develop representative distributions because there is generally too much overlap among the individual distributions, which would make it difficult (if not impossible) to distinguish results plotted on the scales that must be used to capture the full range of results for all air quality scenarios. Representative distributions effectively capture the range of variability in the results for a set of 10 runs.

As discussed in Section 6, all results (both acute and chronic) have been corrected for background ozone levels. Only DFEV results for 8-hr endpoints have been corrected for exercise in clean air for reasons discussed in Section 4.1.

Most figures for acute endpoints contain 6 representative distributions, 1 for each of the 6 air quality scenarios used in this analysis.‡ There are a few exceptions — cases for which only the as-is scenario resulted in measurable risk. (Figure A.10 is an example.)

Figures for chronic endpoints contain 5 representative distributions; in all cases, the distribution for the most stringent standard — Std8506 — results in no risk and is not shown in any of the figures. (If it were shown, it would coincide with the Y-axis.) Only those results

*Avol et al. (1984), Kulle et al. (1985), McDonnell et al. (1983) provide data on heavily exercising individuals, and Seal et al. (1993) provide data on moderately exercising individuals. These data were used to develop 1-hr exposure-response relationships and subsequent risk distributions.

†See Section 6 for discussion about developing representative distributions.

‡Refer to Table 2.5 for definitions of the 6 air quality scenarios, 5 of which represent attainment of specific air quality standards.

based on the judgments of Expert A are shown. Results for other experts are available but are not included in this report.

The subtitle for each figure contains a code that identifies the health endpoint associated with the figure. The figure caption essentially interprets the code. For acute endpoints, a 7-character code (e.g., AF101LT) indicates the study (A = Avol, K = Kulle, M = McDonnell, S = Seal, and C = combined*), the health endpoint (F10 = FEV $\geq$ 10%), the number of hours of exposure (1), the city (L = Los Angeles, N = New York City), and the population (T = total population). For chronic endpoints, a 5-character code denotes the expert on whose judgments results are based, the lesion type, the city, the population of interest, and the number of ozone seasons of exposure. For example, AILC1 denotes expert A, mild[†] lesions, Los Angeles, Children, and 1 season[‡] of exposure.

These results could have been presented in tables like Table 6.1 rather than in figures. The drawback of tabular results is that one page is needed per air quality scenario. The figures presented here display results for as many as 6 air quality scenarios, which considerably reduces the number of pages needed to present results.

*That is, the studies conducted by Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991).

[†]The letter "O" in this character position denotes moderate lesions.

[‡]The letter "T" in this character position denotes Ten ozone seasons.

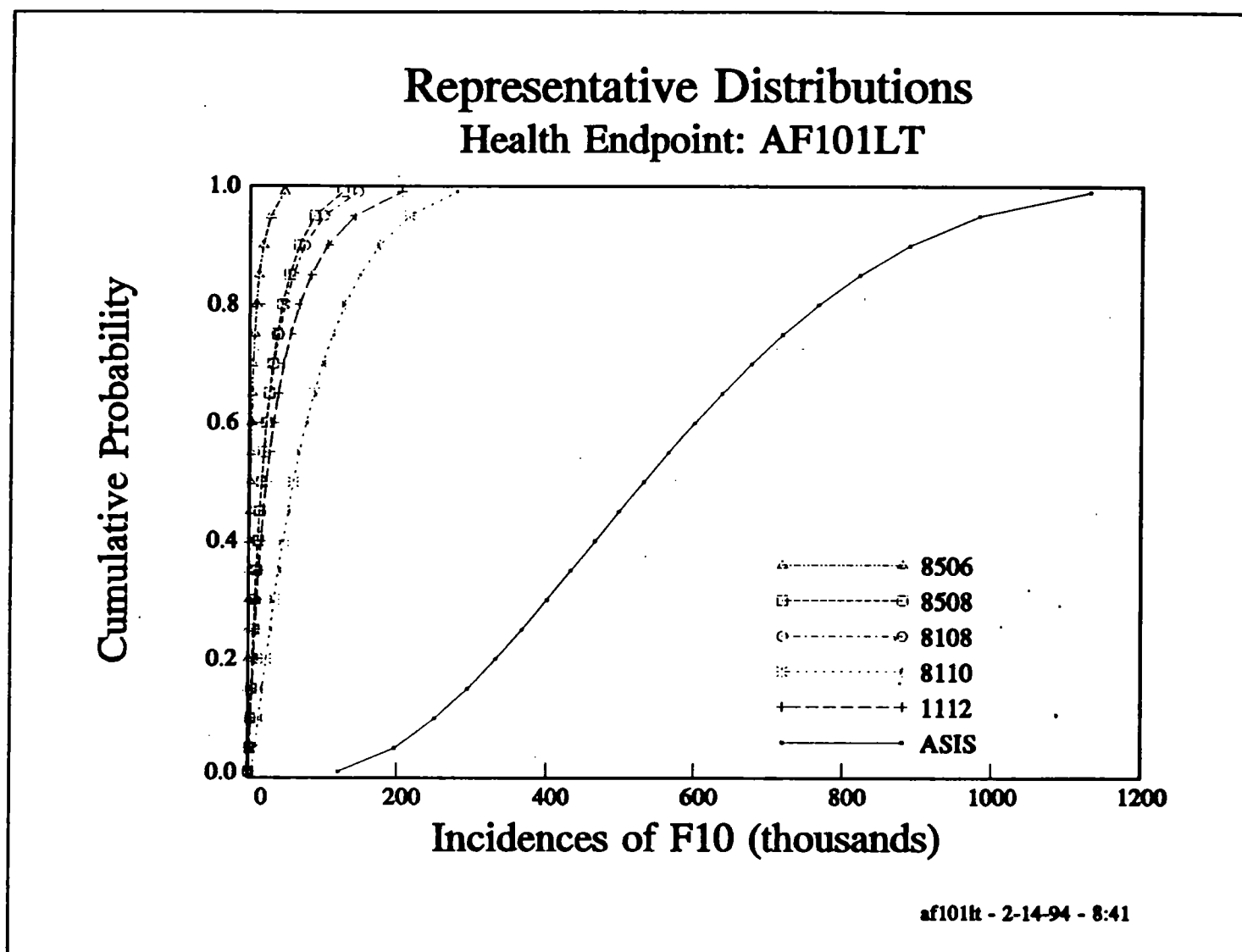


FIGURE A.1 Risk Distributions for FEV Decrements $\geq 10\%$ Based on Data from the Avol et al. (1984) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

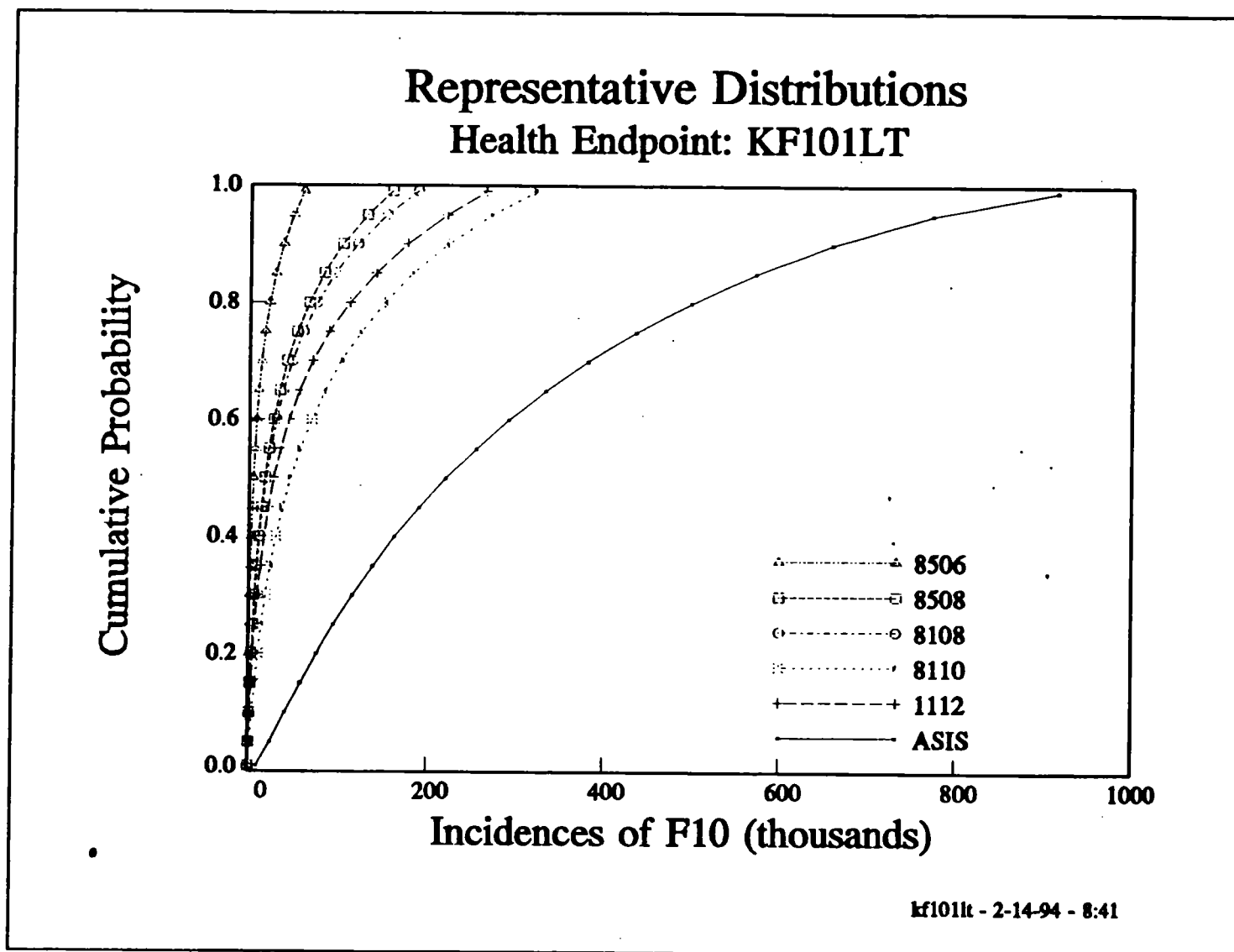


FIGURE A.2 Risk Distributions for FEV Decrements $\geq 10\%$ Based on Data from the Kulle et al. (1985) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

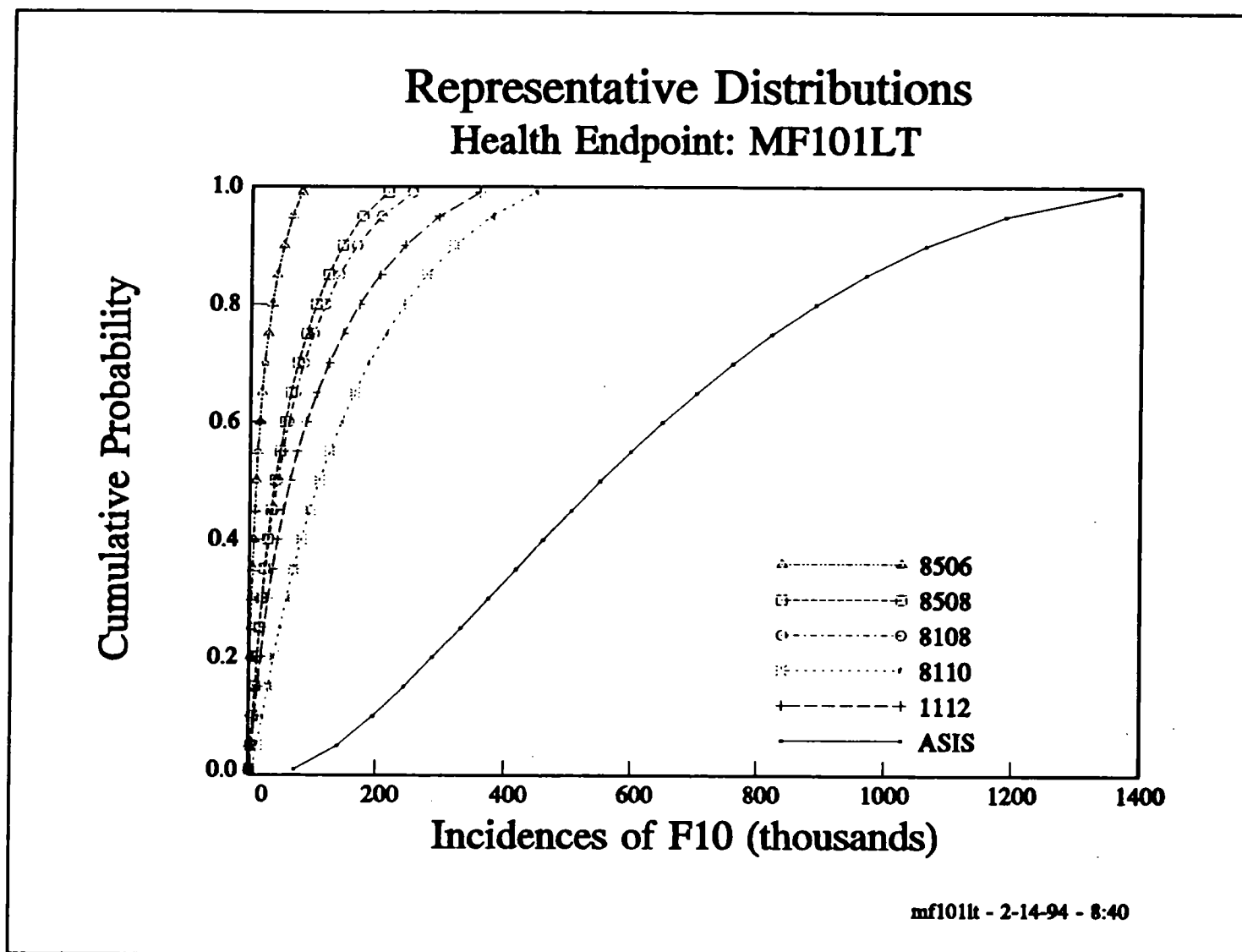


FIGURE A.3 Risk Distributions for FEV Decrement $\geq 10\%$ Based on Data from the McDonnell et al. (1983) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

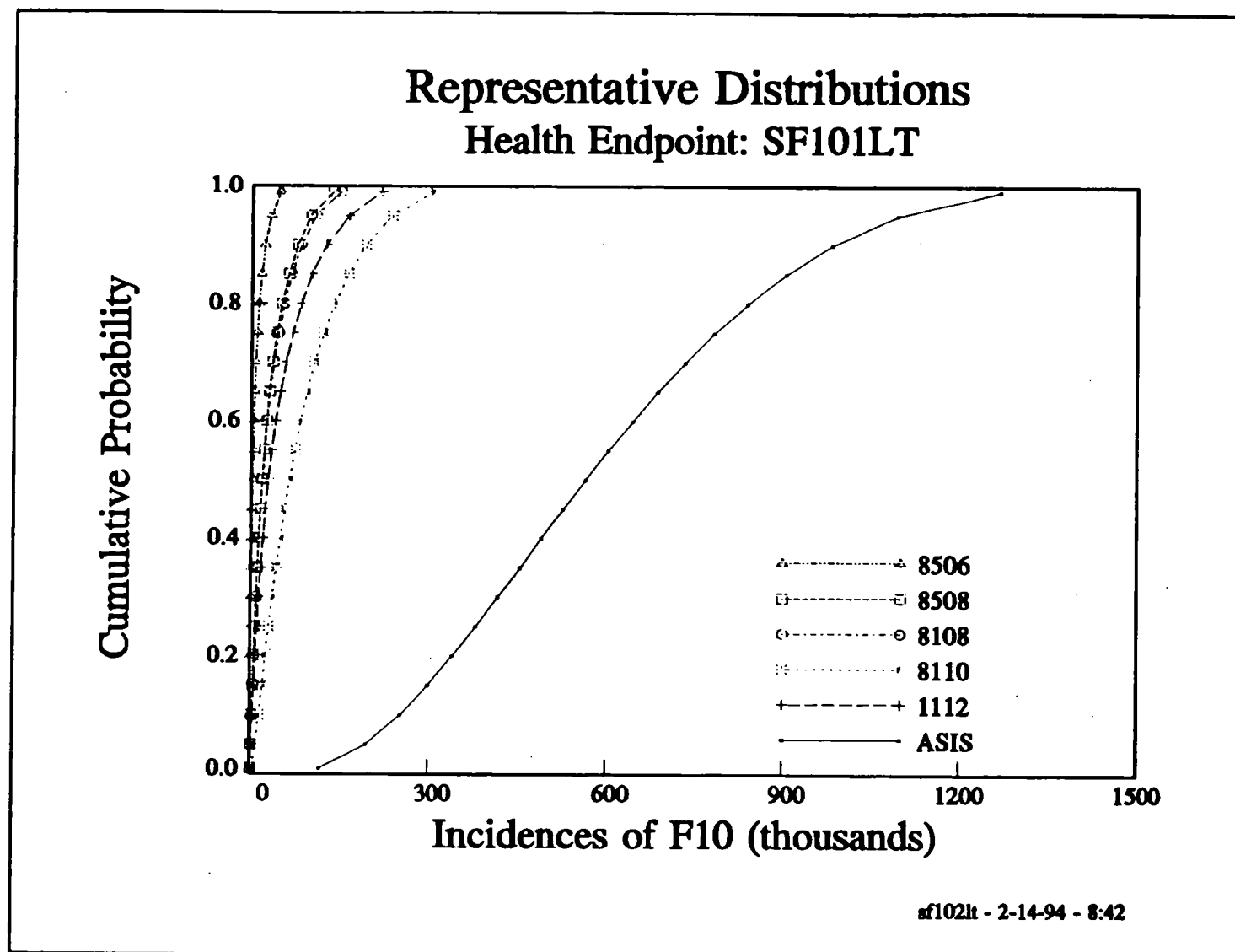


FIGURE A.4 Risk Distributions for FEV Decrement $\geq 10\%$ Based on Data from the Seal et al. (1993) Study (1-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

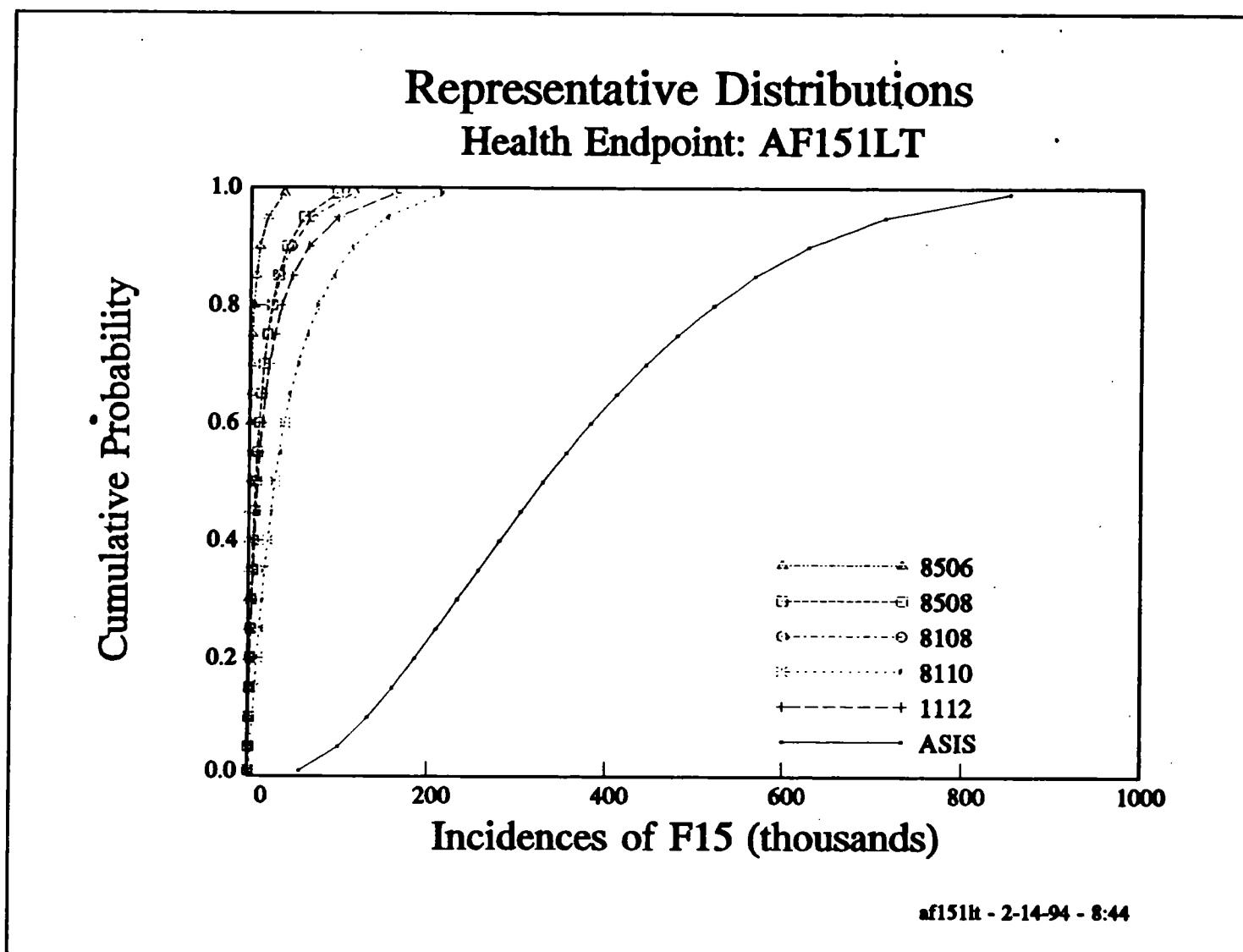


FIGURE A.5 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the Avol et al. (1984) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

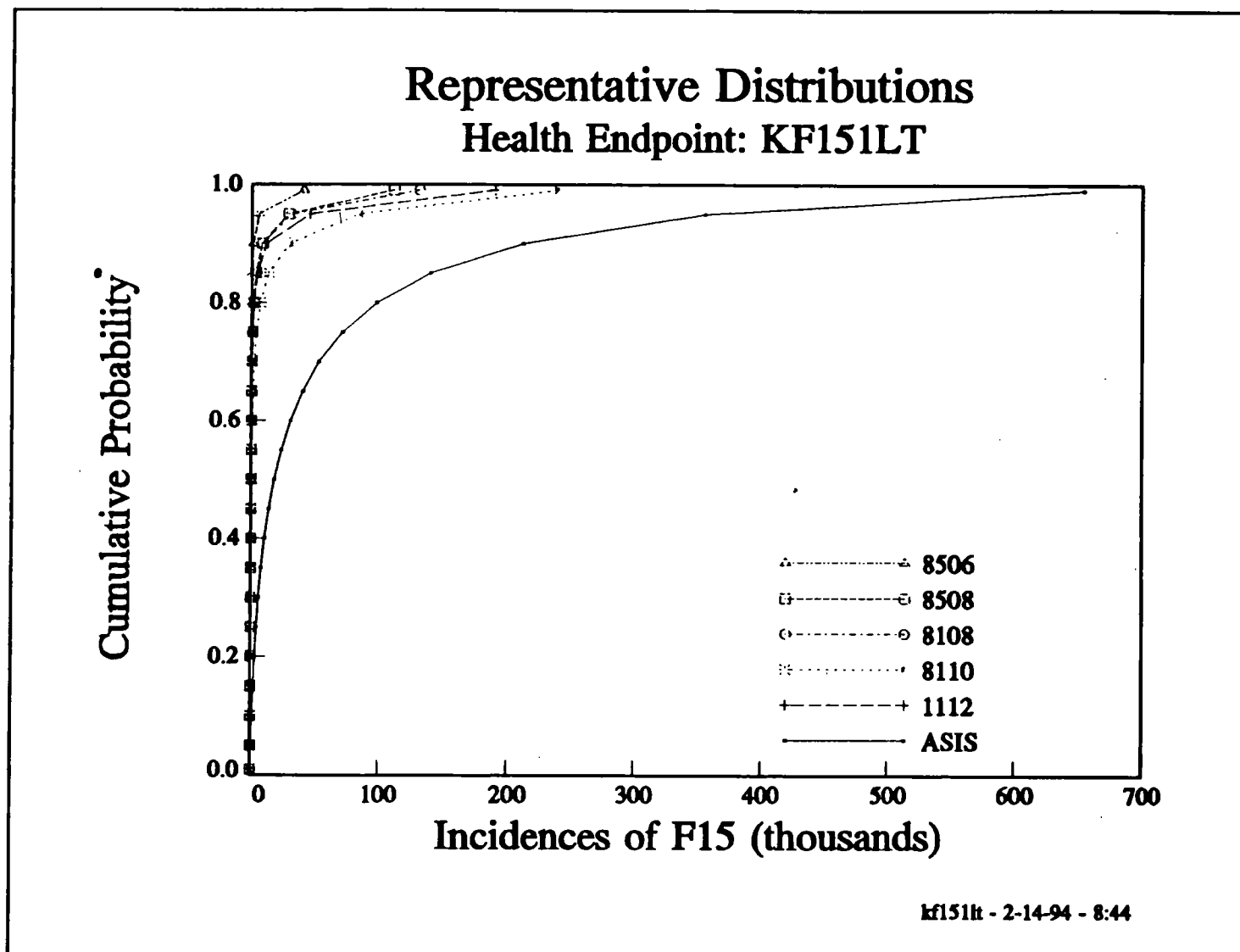


FIGURE A.6 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the Kulle et al. (1985) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

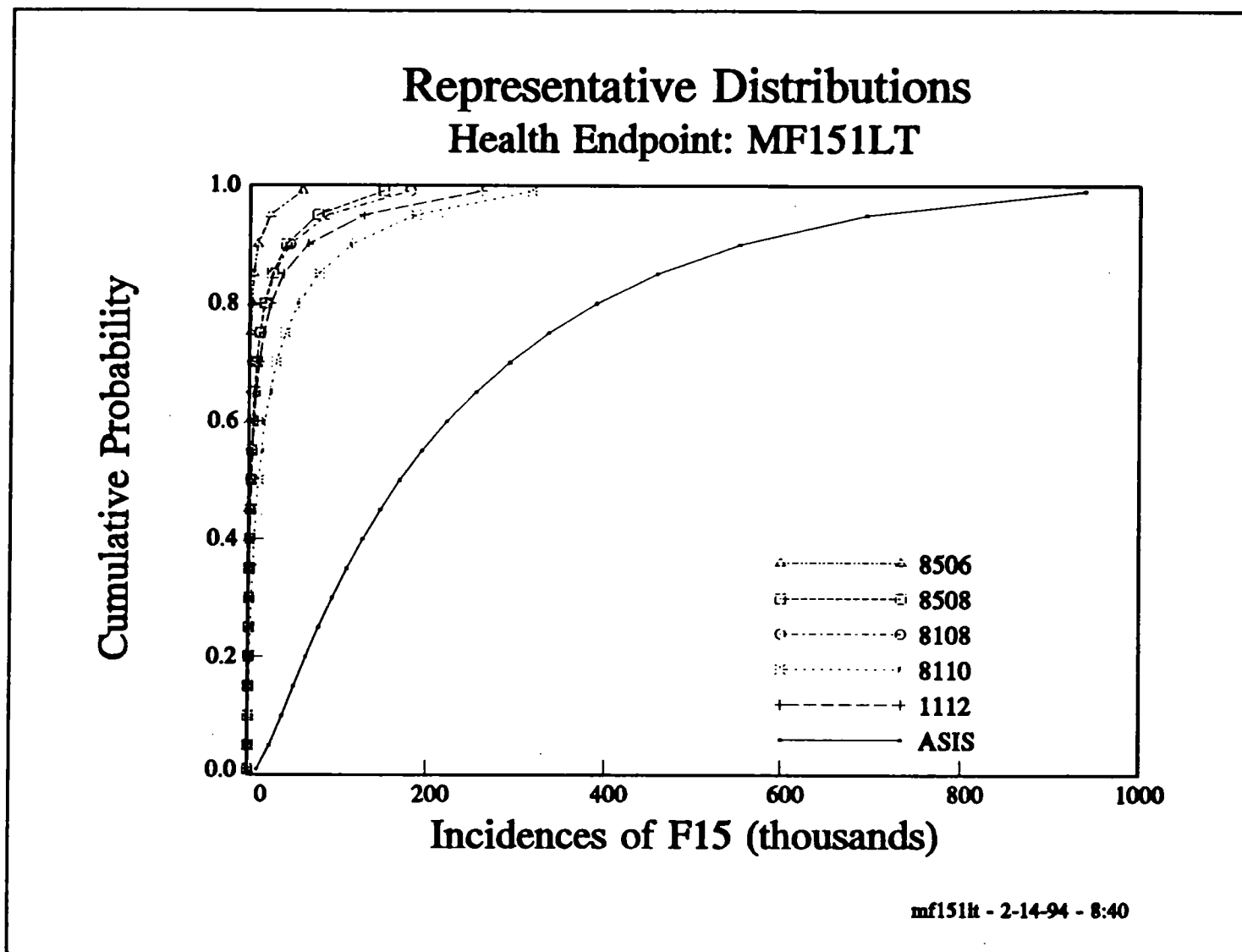


FIGURE A.7 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the McDonnell et al. (1983) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

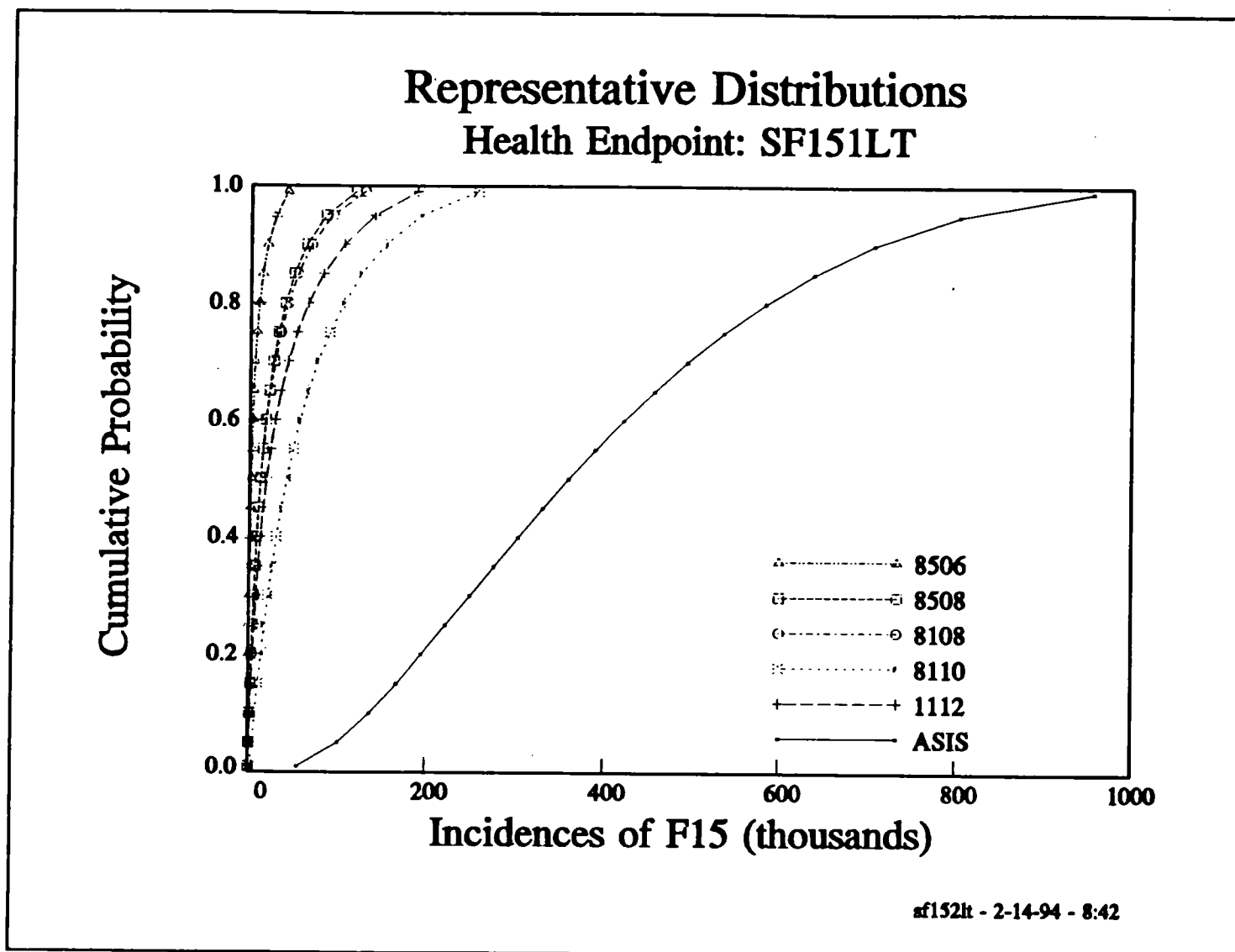


FIGURE A.8 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the Seal et al. (1993) Study (1-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

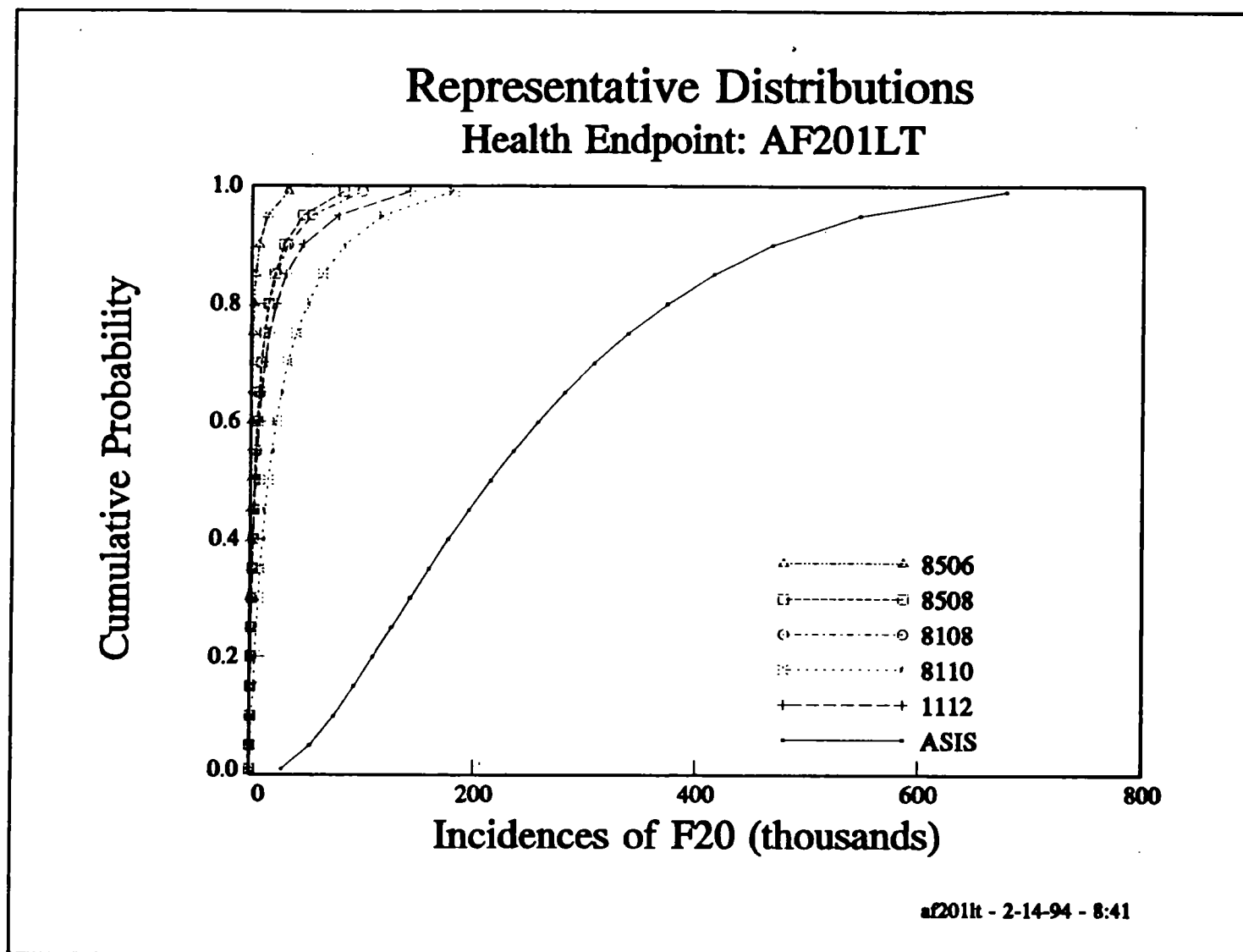


FIGURE A.9 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the Avol et al. (1984) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

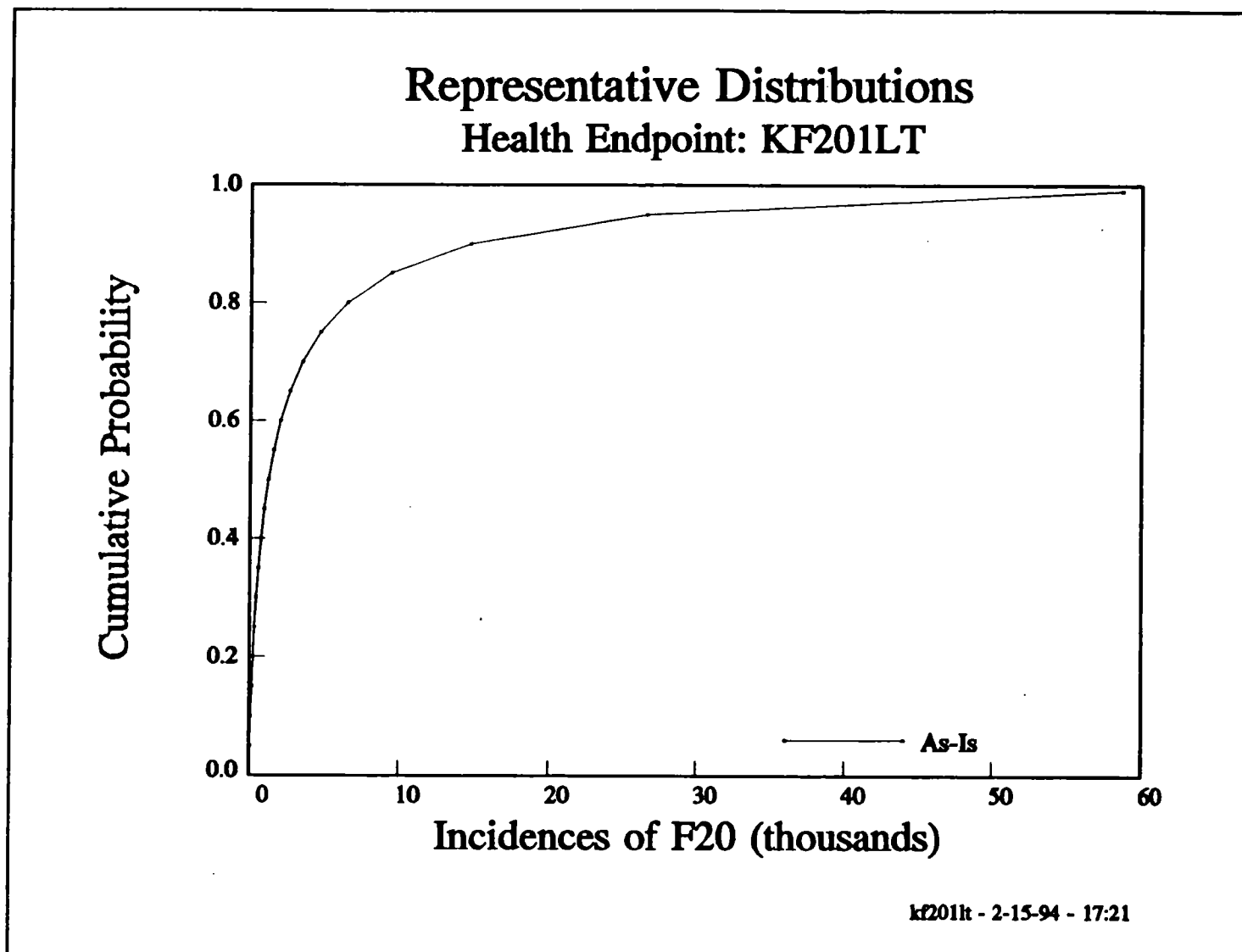


FIGURE A.10 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the Kulle et al. (1985) Study (1-hour exposures at heavy exercise, Los Angeles, total population, as-is air quality [the only non-zero risk distribution])

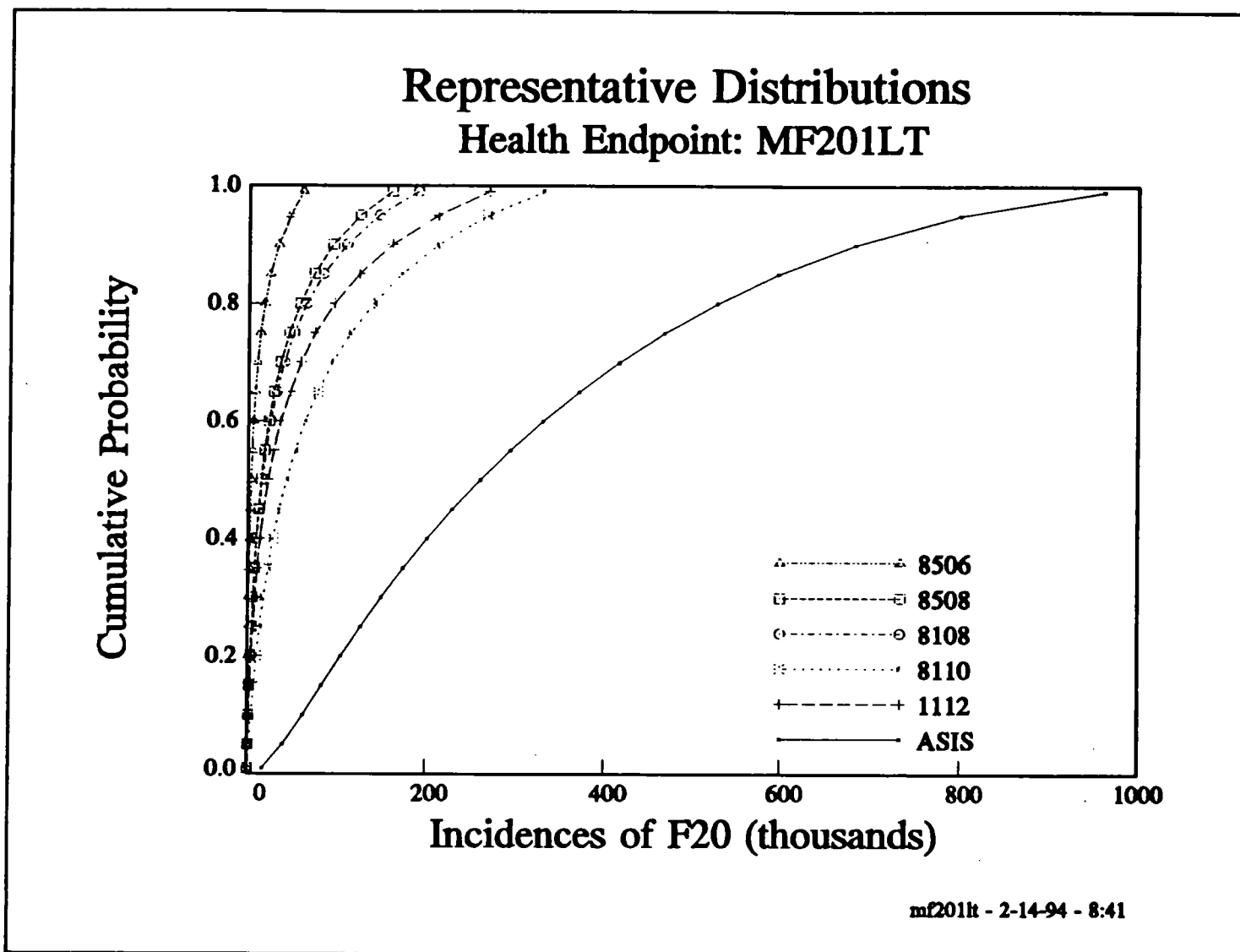


FIGURE A.11 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the McDonnell et al. (1983) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

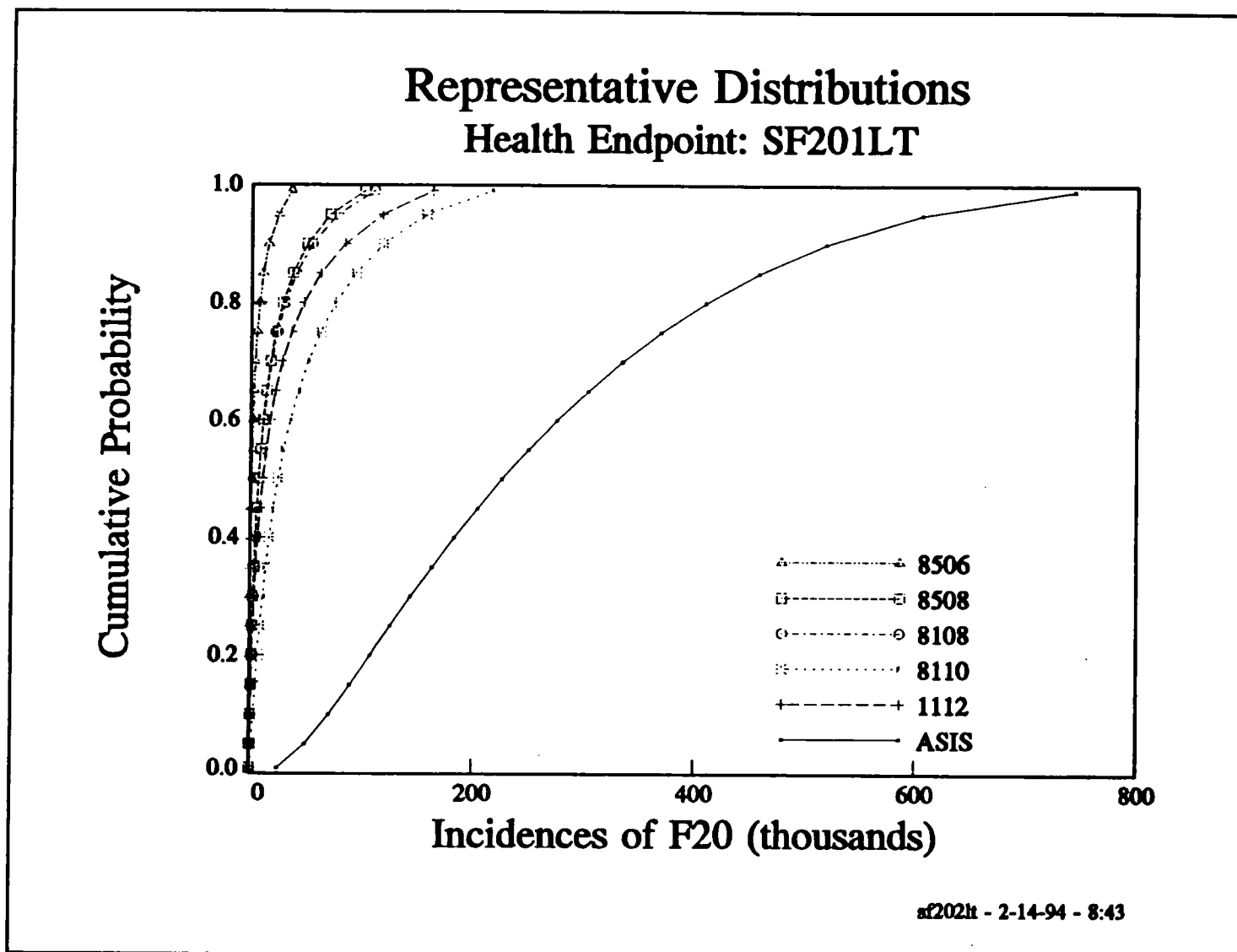


FIGURE A.12 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the Seal et al. (1993) Study (1-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

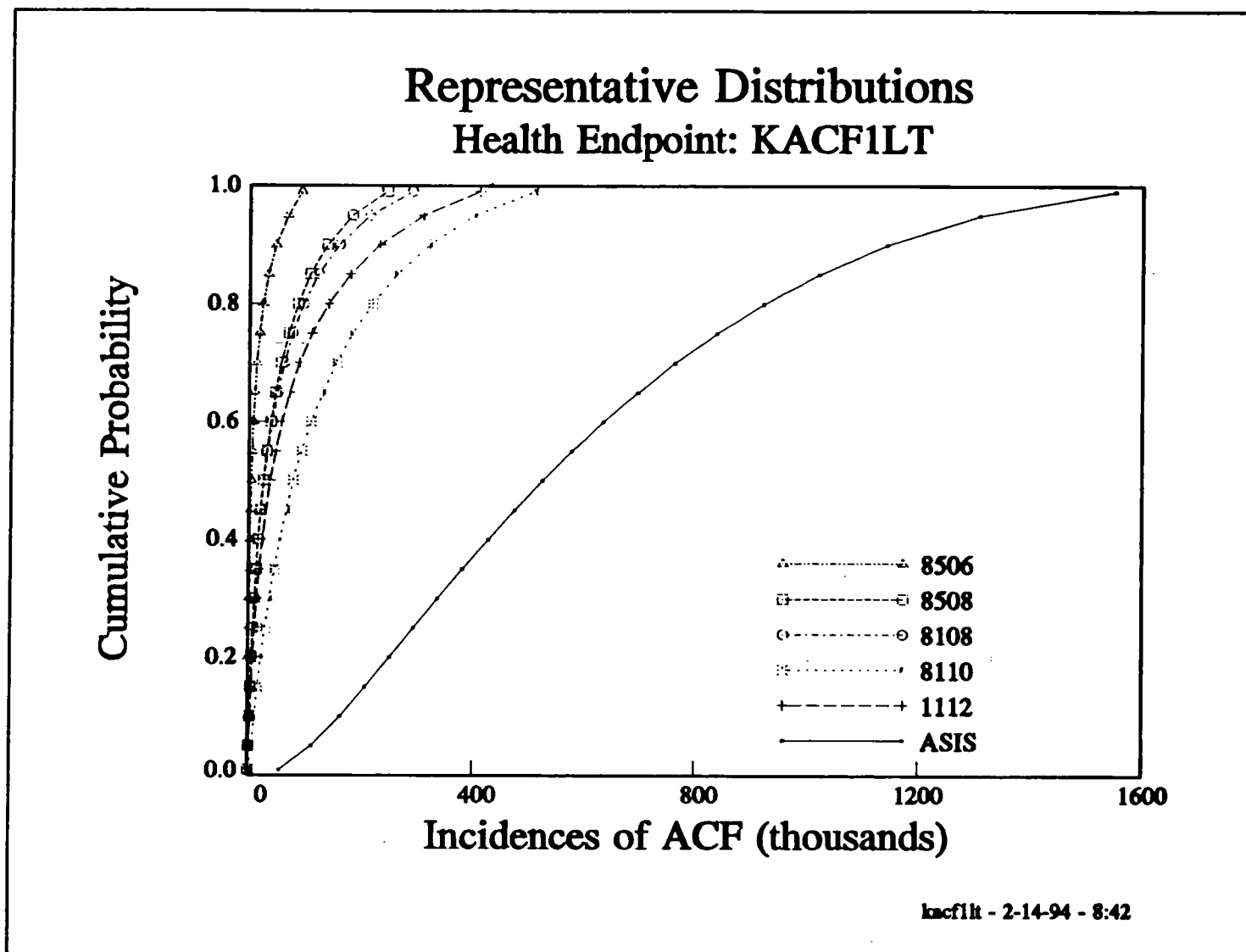


FIGURE A.13 Risk Distributions for Any Cough Based on Data from the Kulle et al. (1985) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

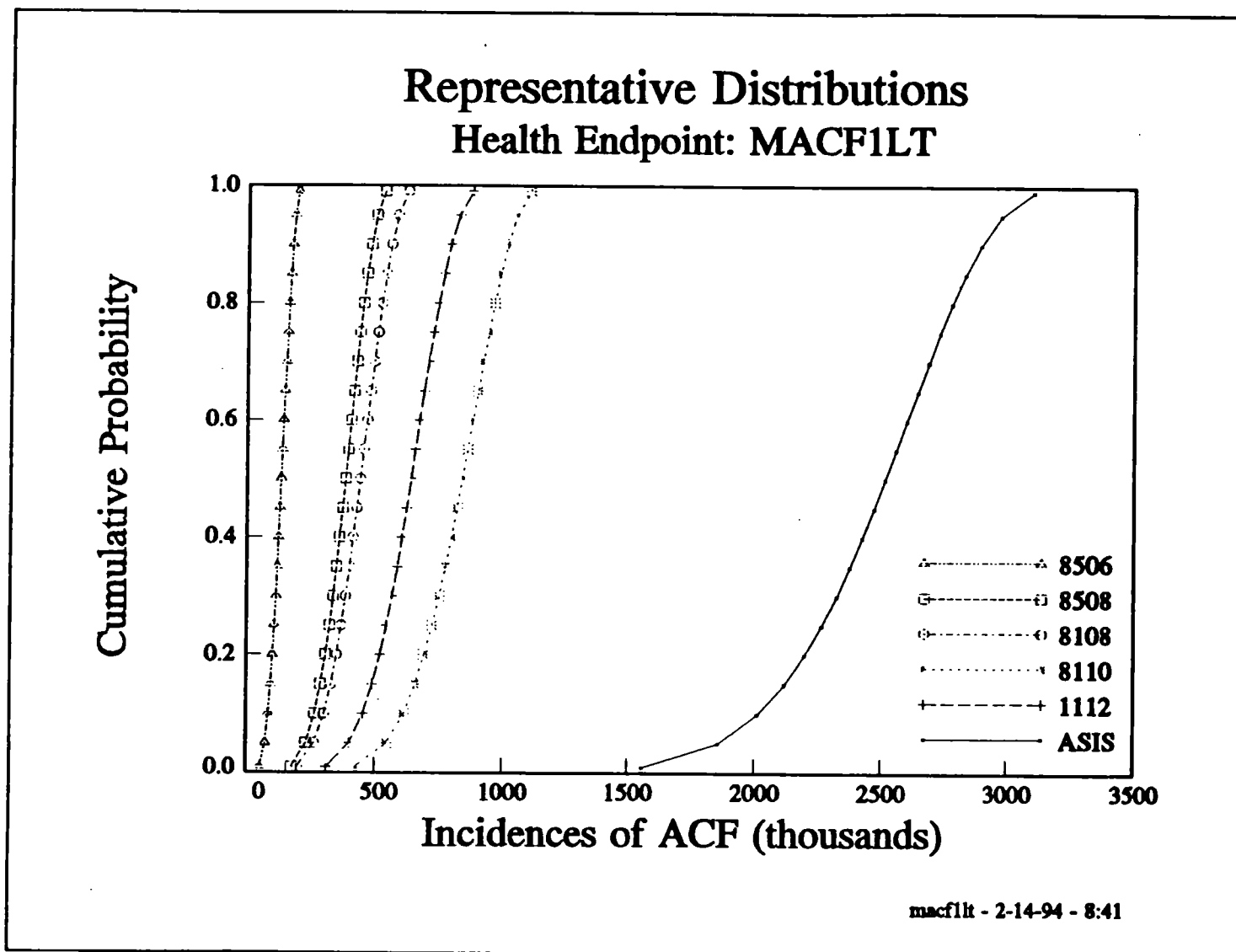


FIGURE A.14 Risk Distributions for Any Cough Based on Data from the McDonnell et al. (1983) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

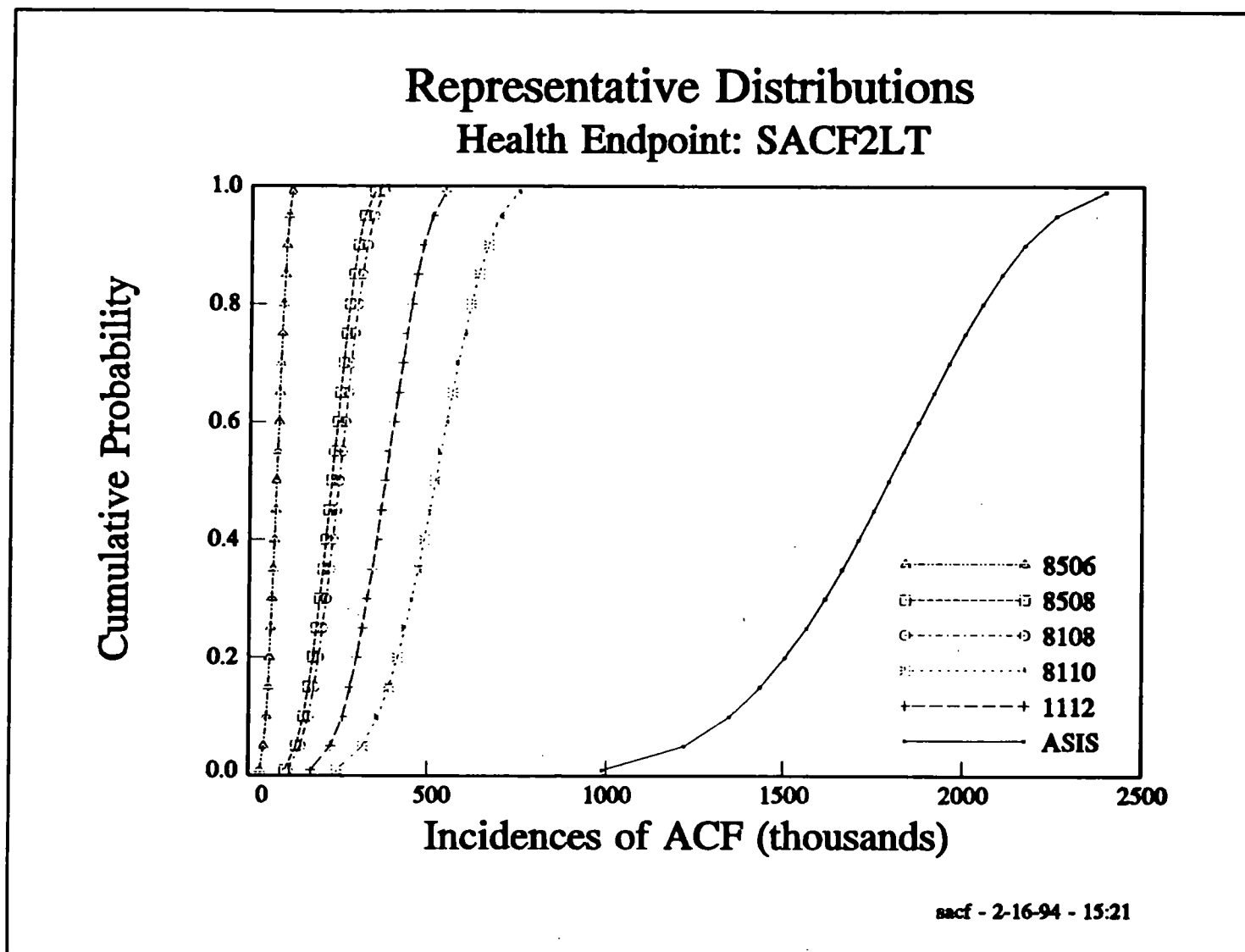


FIGURE A.15 Risk Distributions for Any Cough Based on Data from the Seal et al. (1993) Study (1-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

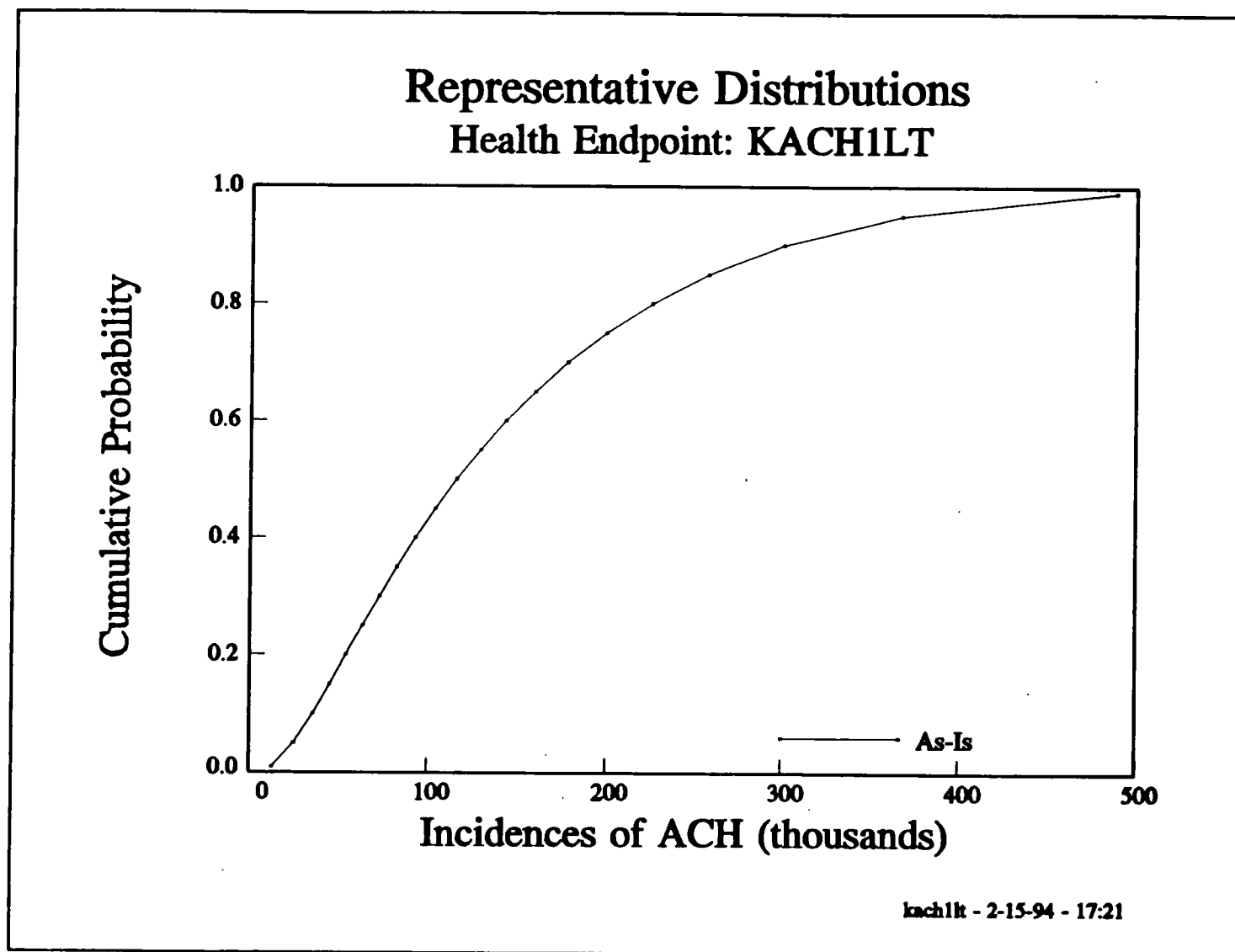


FIGURE A.16 Risk Distributions for Any Chest Discomfort Based on Data from the Kulle et al. (1985) Study (1-hour exposures at moderate exercise, Los Angeles, total population, as-is air quality [the only non-zero risk distribution])

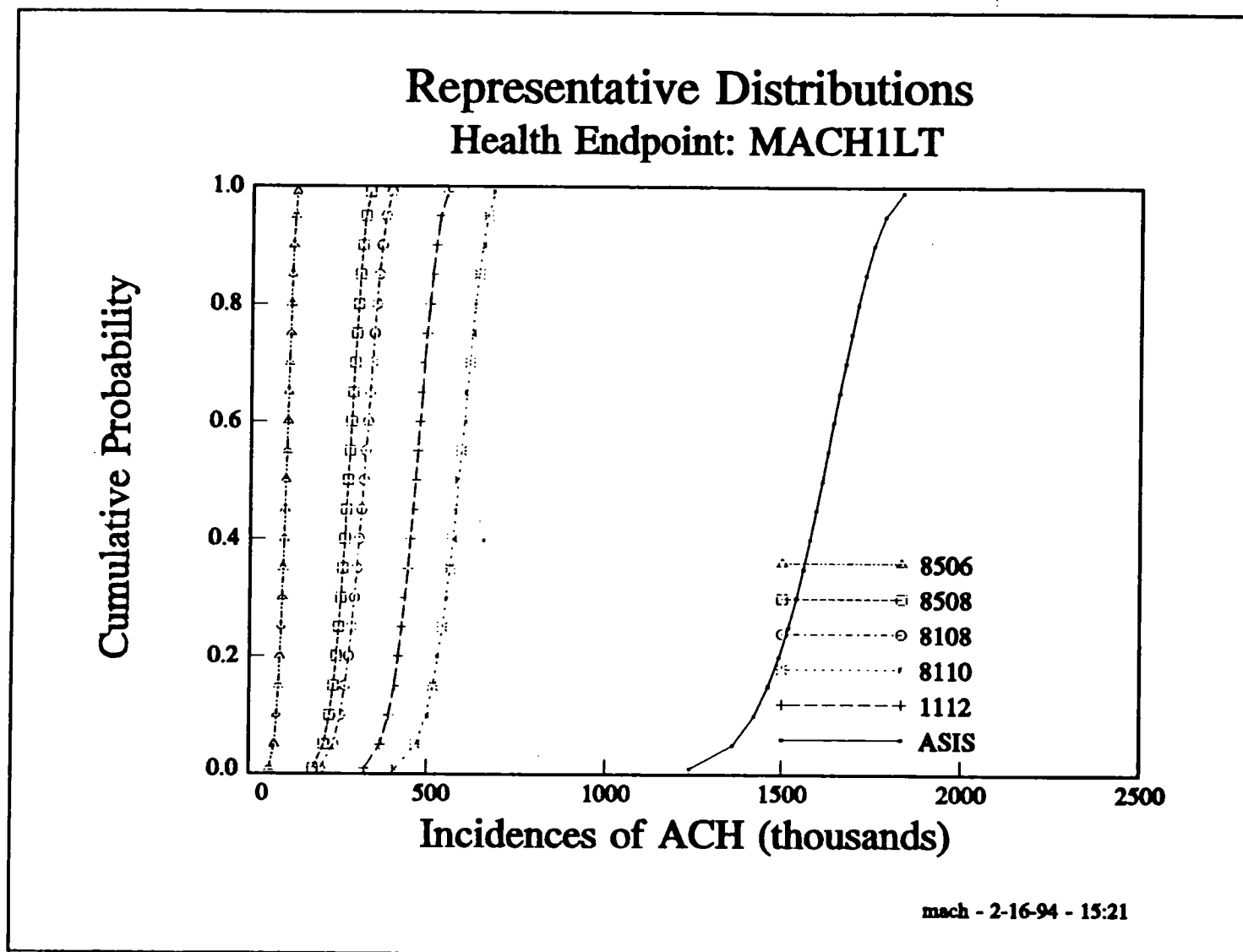


FIGURE A.17 Risk Distributions for Any Chest Discomfort Based on Data from the McDonnell et al. (1983) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

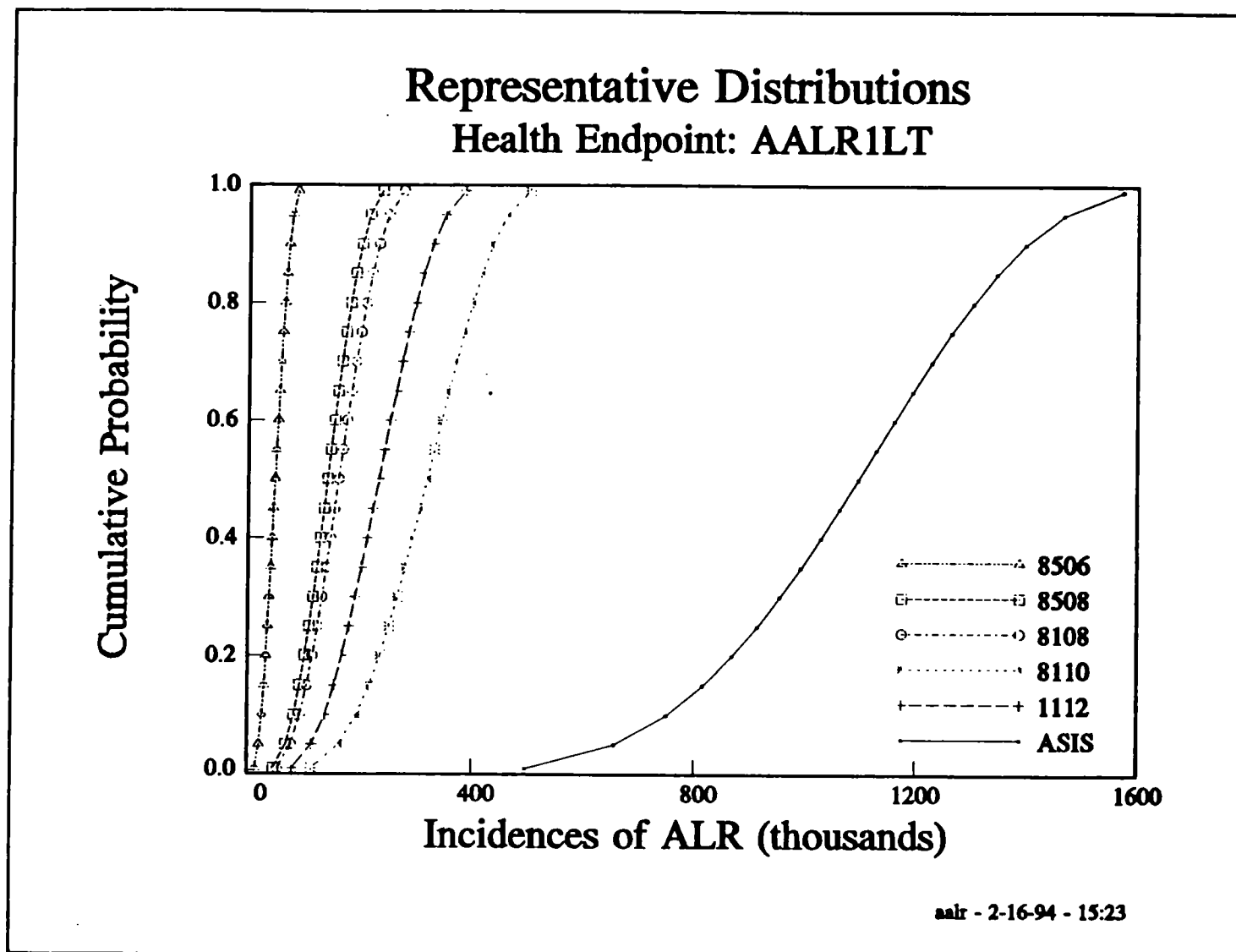


FIGURE A.18 Risk Distributions for Any Lower Respiratory Symptoms Based on Data from the Avol et al. (1984) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

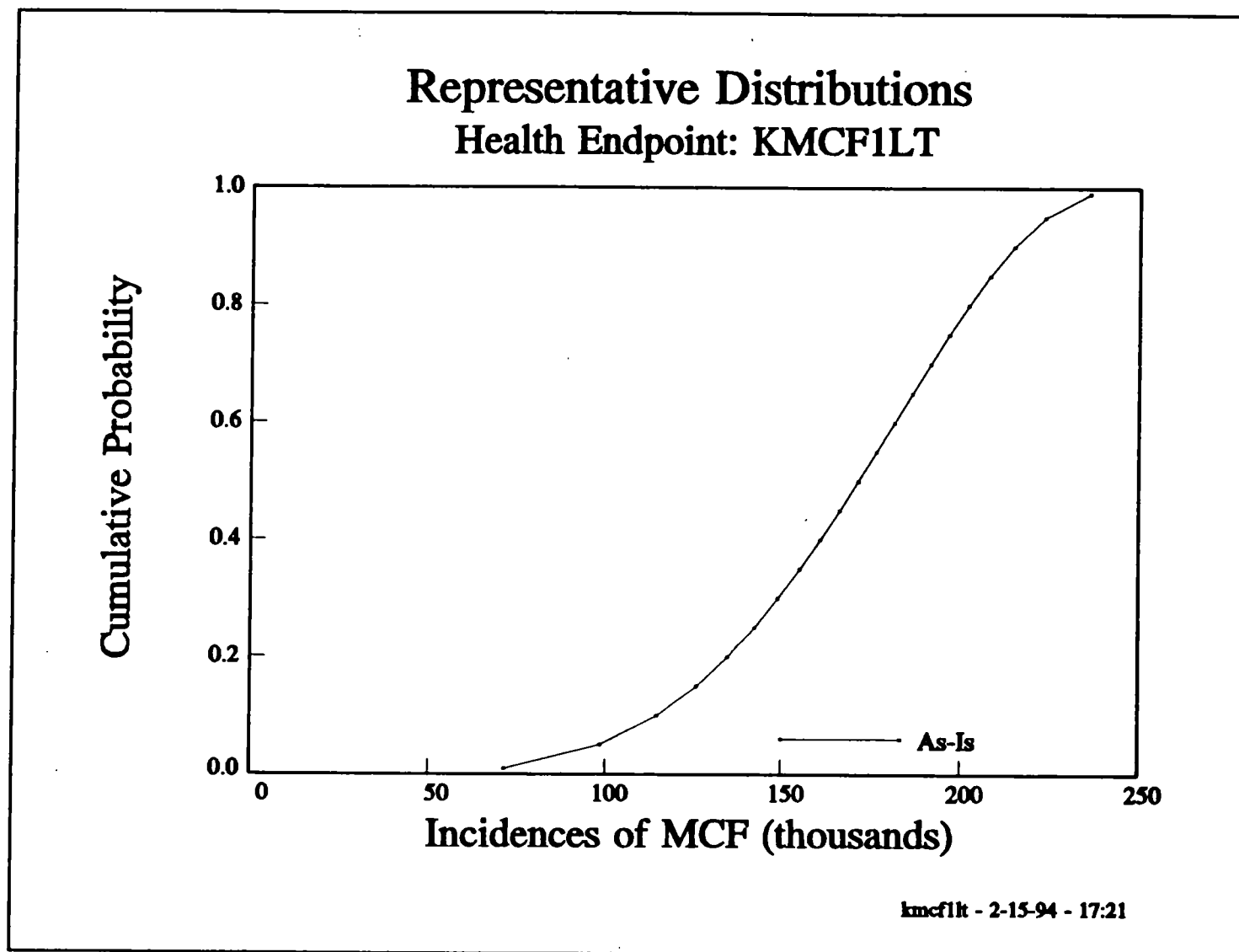


FIGURE A.19 Risk Distributions for Moderate/Severe Cough Based on Data from the Kulle et al. (1985) Study (1-hour exposures at heavy exercise, Los Angeles, total population, as-is air quality [the only non-zero risk distribution])

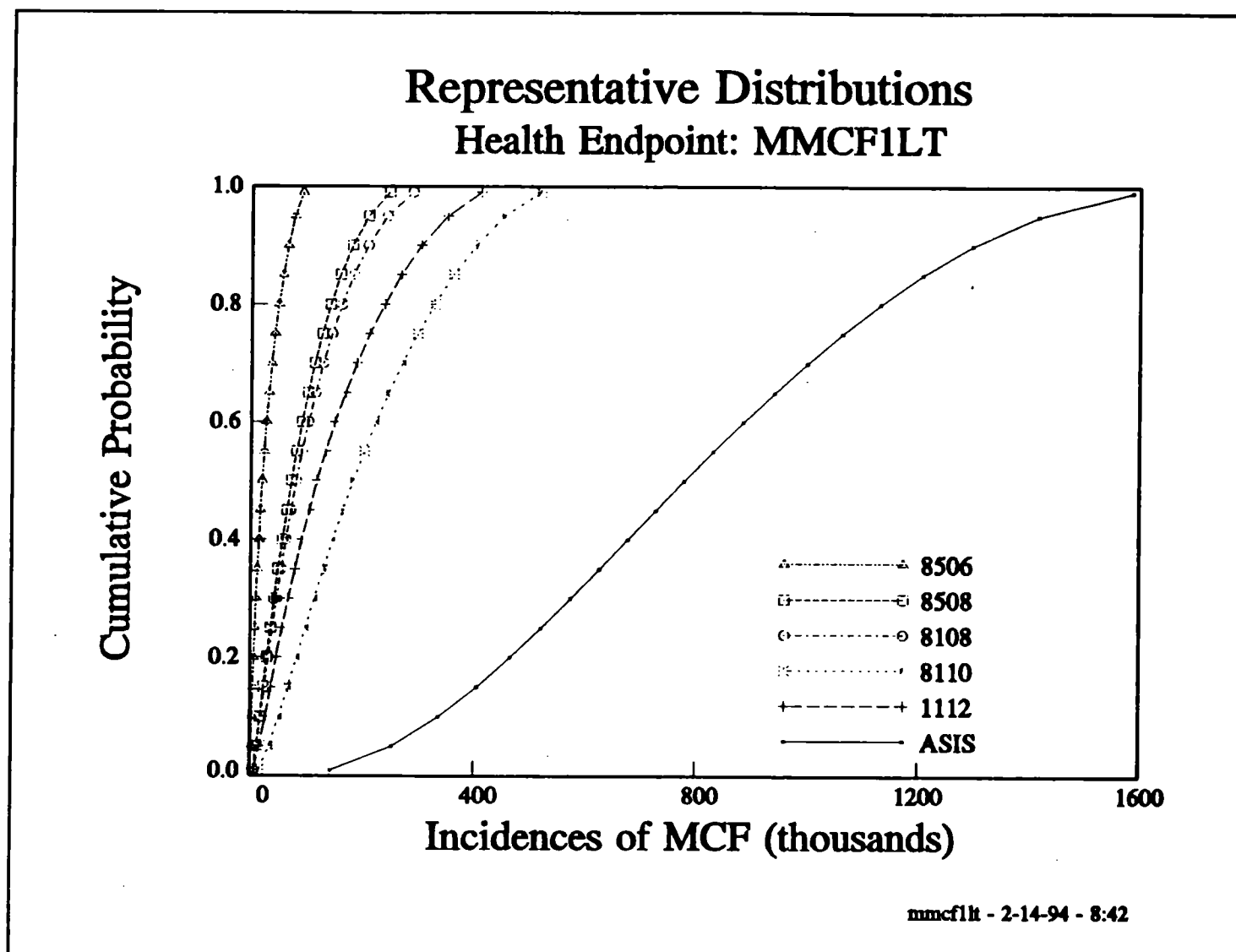


FIGURE A.20 Risk Distributions for Moderate/Severe Cough Based on Data from the McDonnell et al. (1983) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

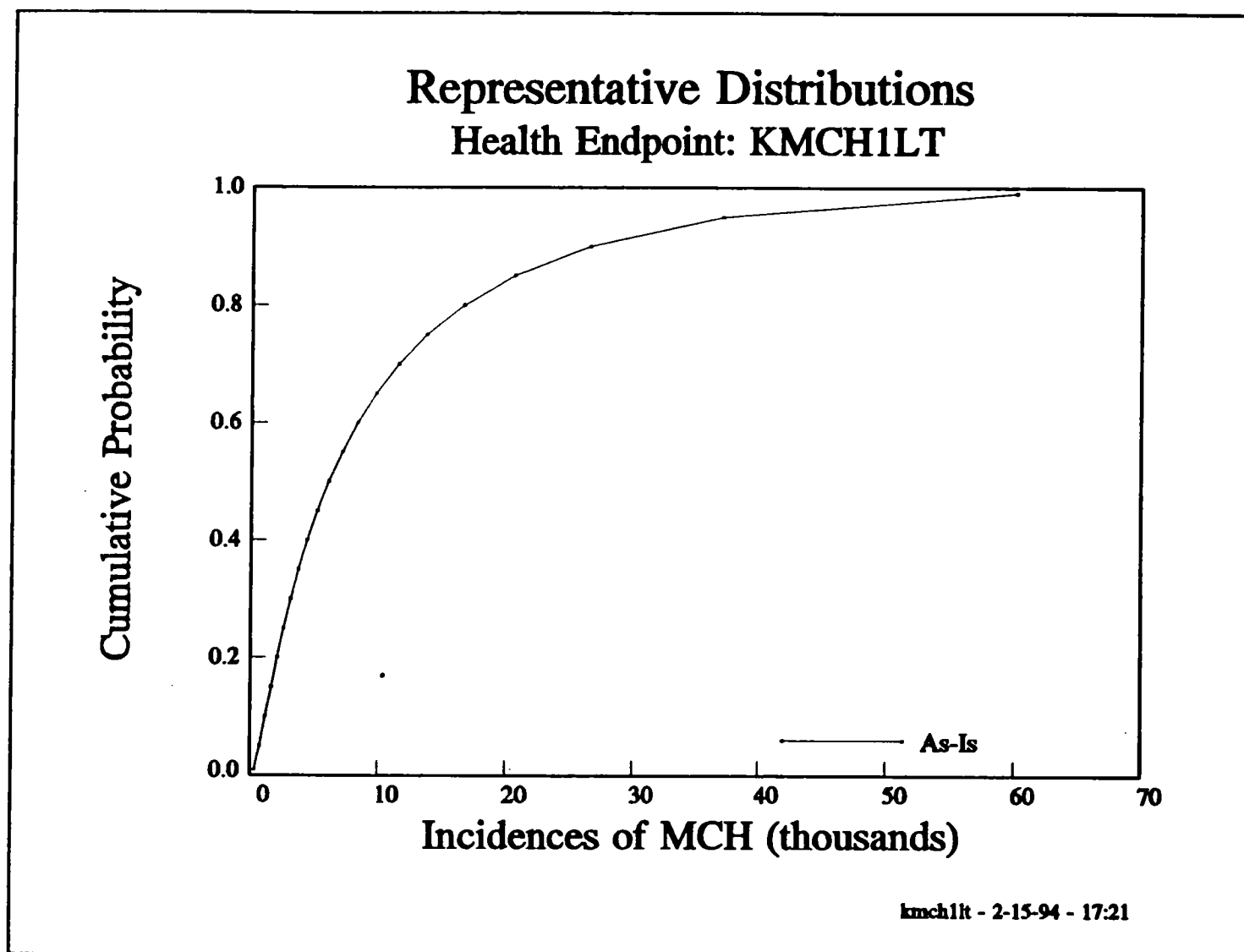


FIGURE A.21 Risk Distributions for Moderate/Severe Chest Discomfort Based on Data from the Kulle et al. (1985) Study (1-hour exposures at heavy exercise, Los Angeles, total population, as-is air quality [the only non-zero risk distribution])

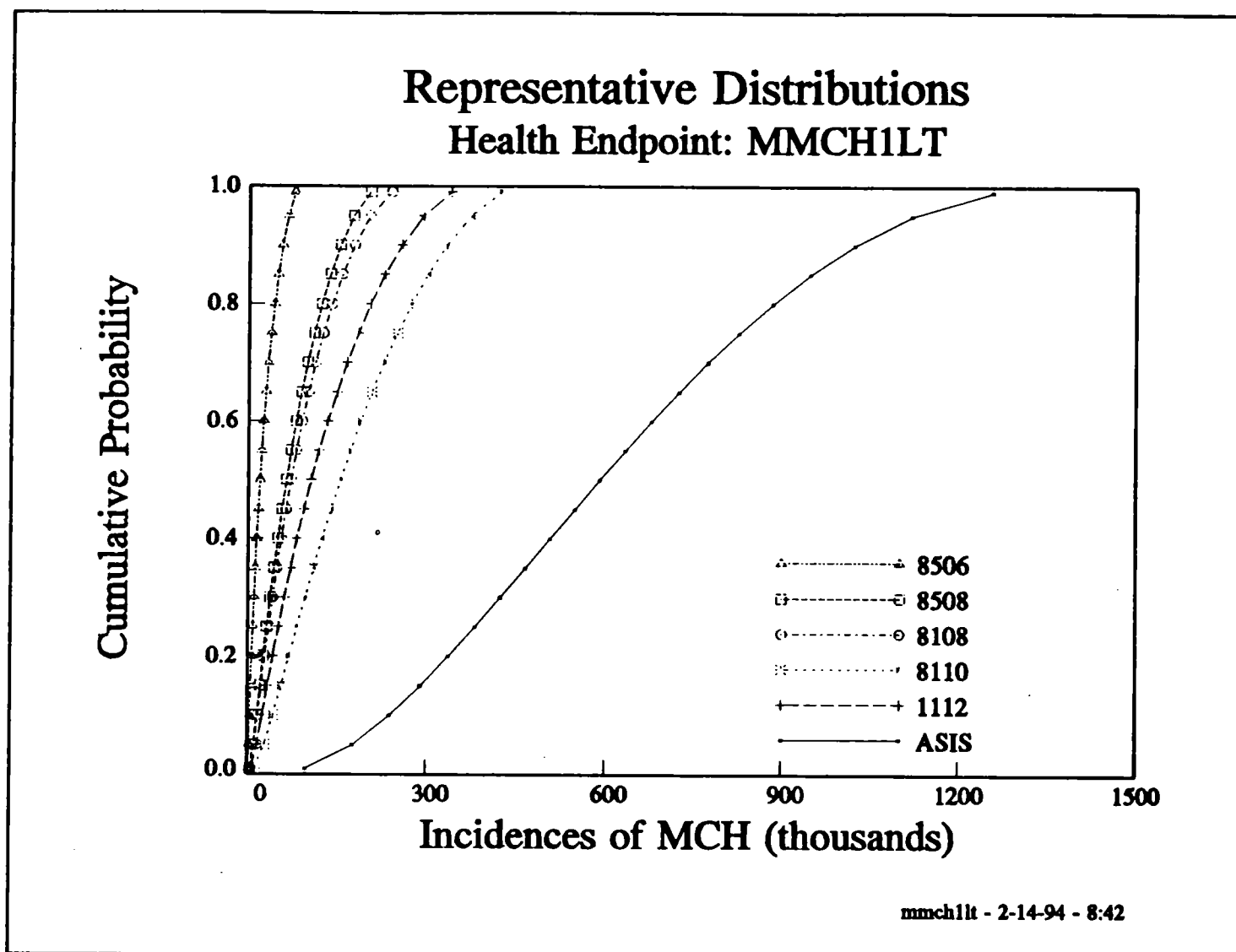


FIGURE A.22 Risk Distributions for Moderate/Severe Chest Discomfort Based on Data from the McDonnell et al. (1983) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

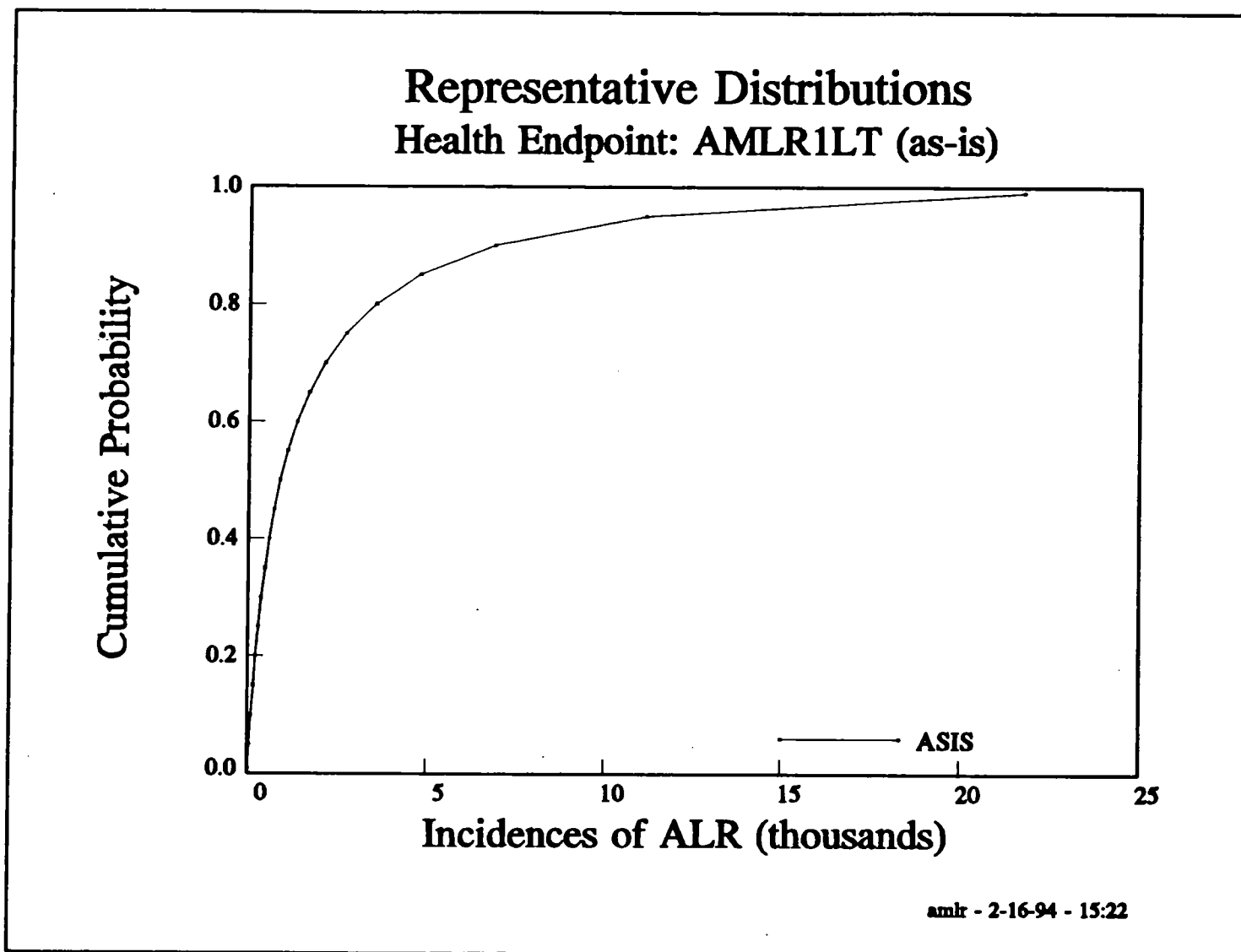


FIGURE A.23 Risk Distributions for Moderate/Severe Lower Respiratory Symptoms Based on Data from the Avol et al. (1984) Study (1-hour exposures at heavy exercise, Los Angeles, total population, all air quality scenarios)

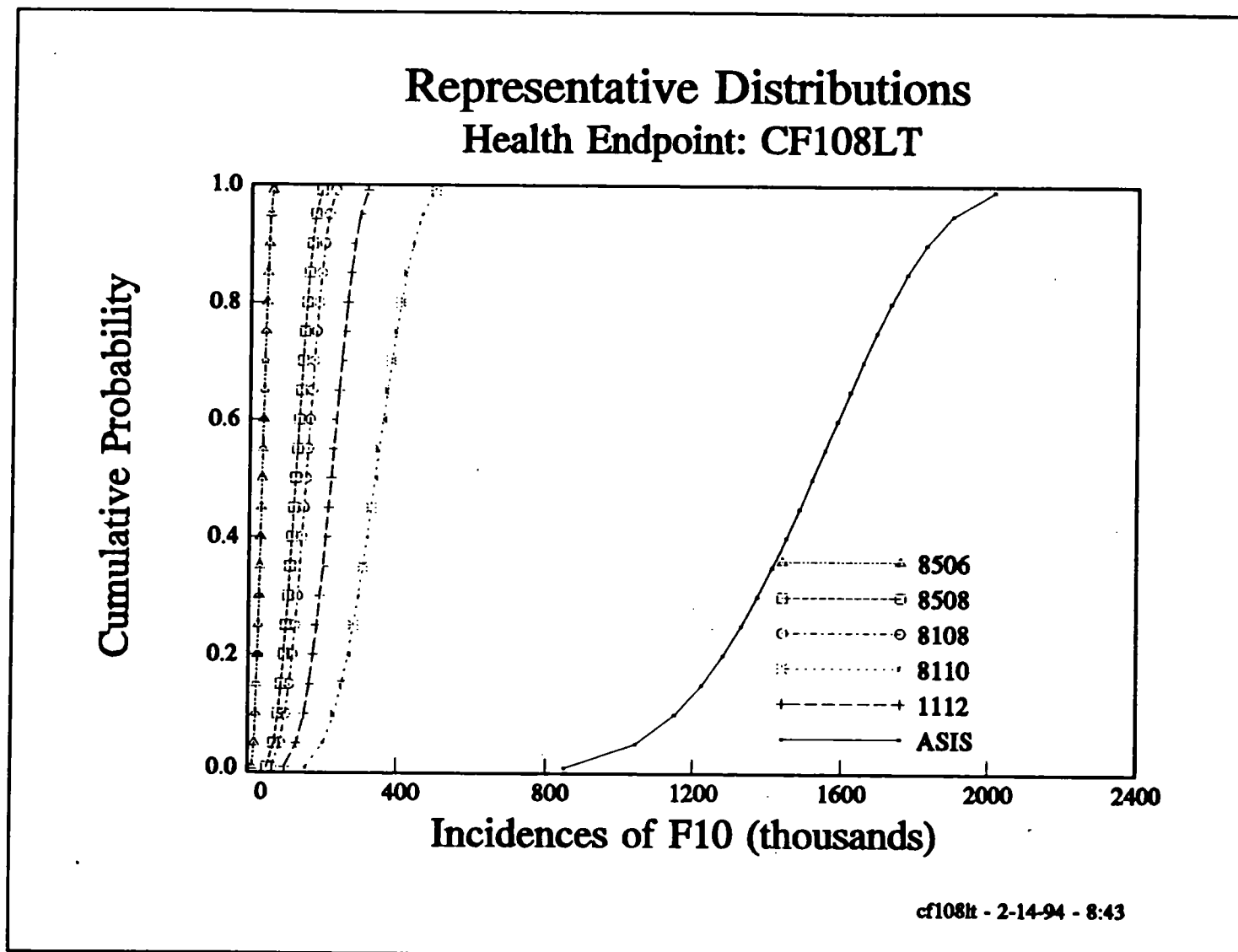


FIGURE A.24 Risk Distributions for FEV Decrement $\geq 10\%$ Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies (8-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

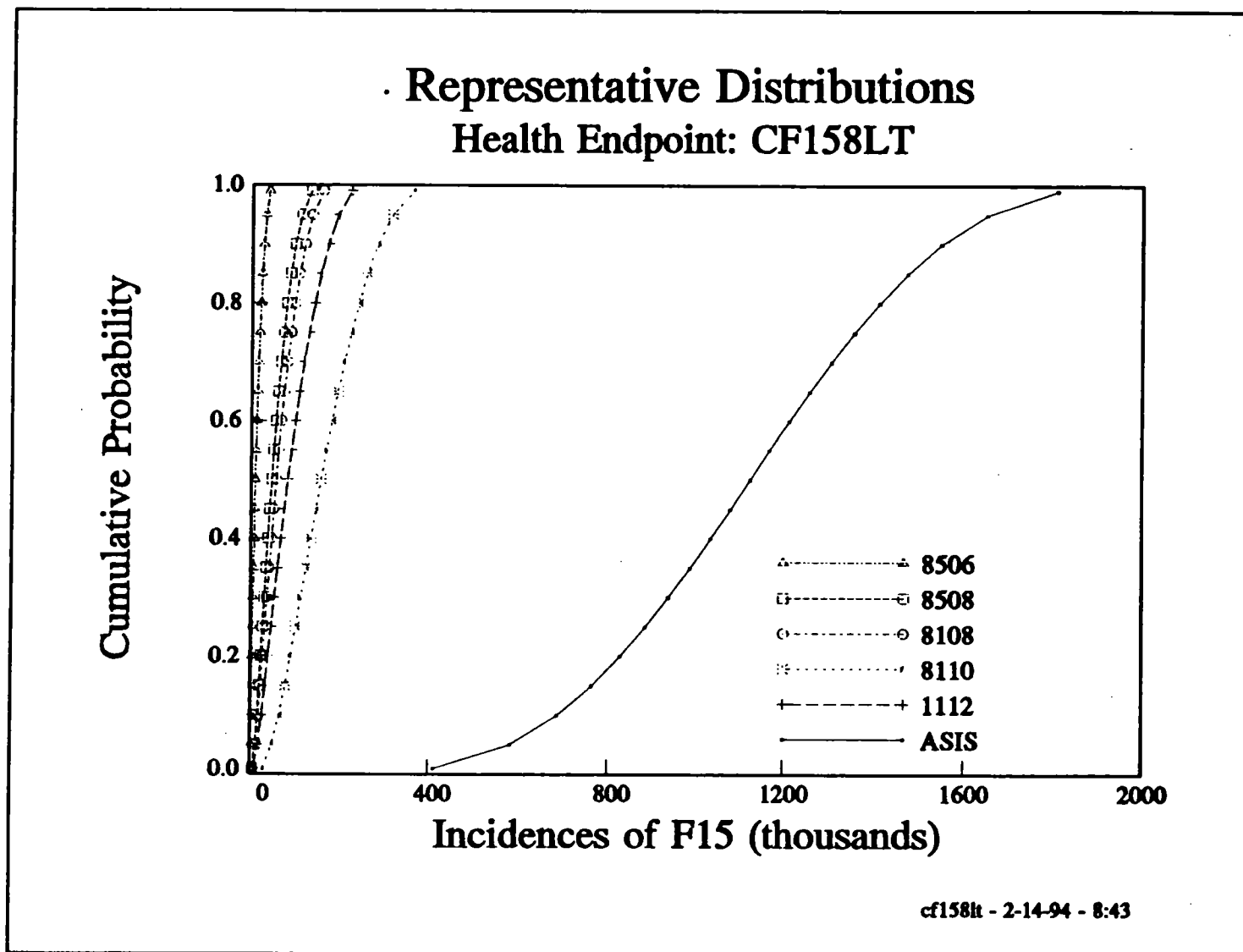


FIGURE A.25 Risk Distributions for FEV Decrement $\geq 15\%$ Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies (8-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

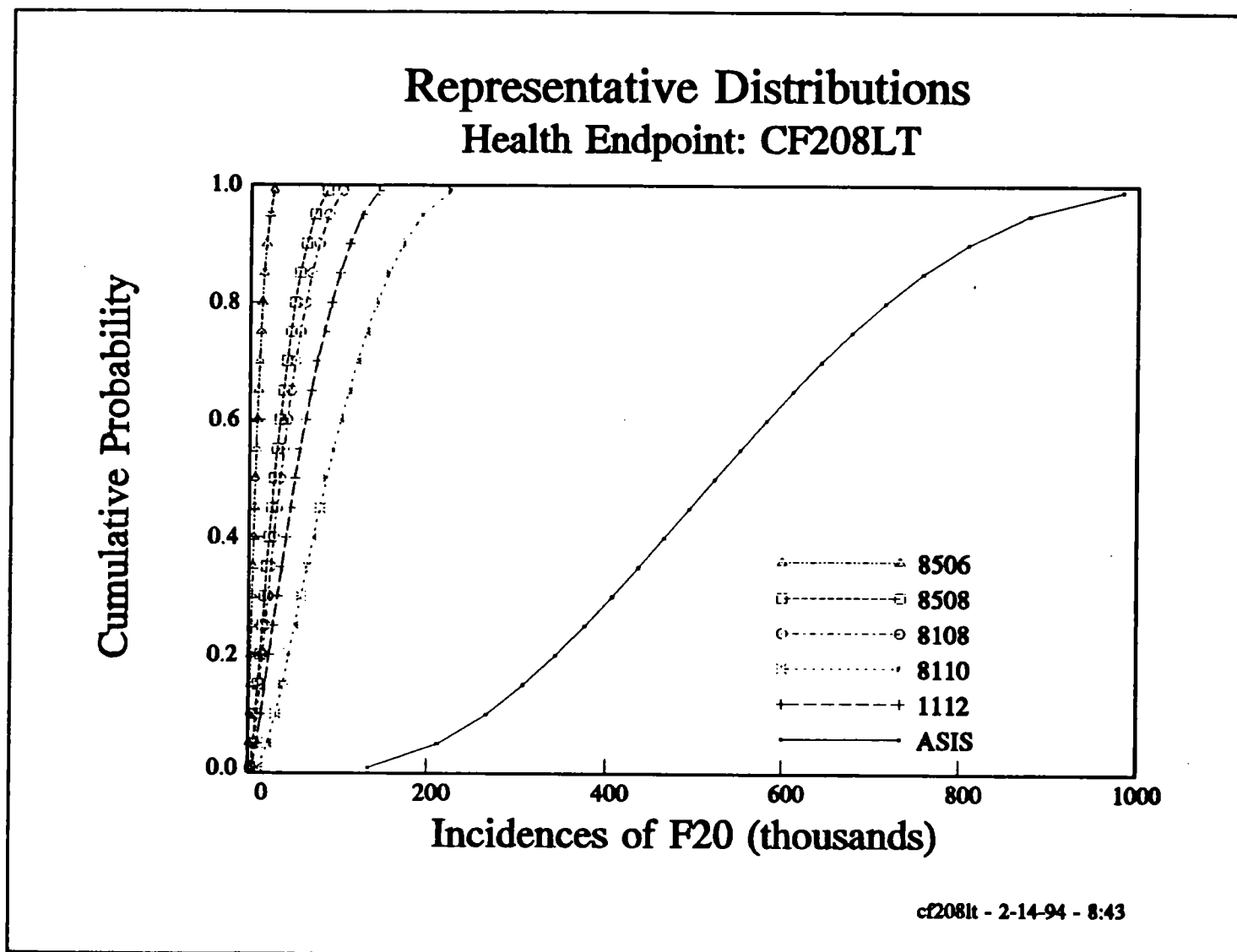


FIGURE A.26 Risk Distributions for FEV Decrement $\geq 20\%$ Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies (8-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

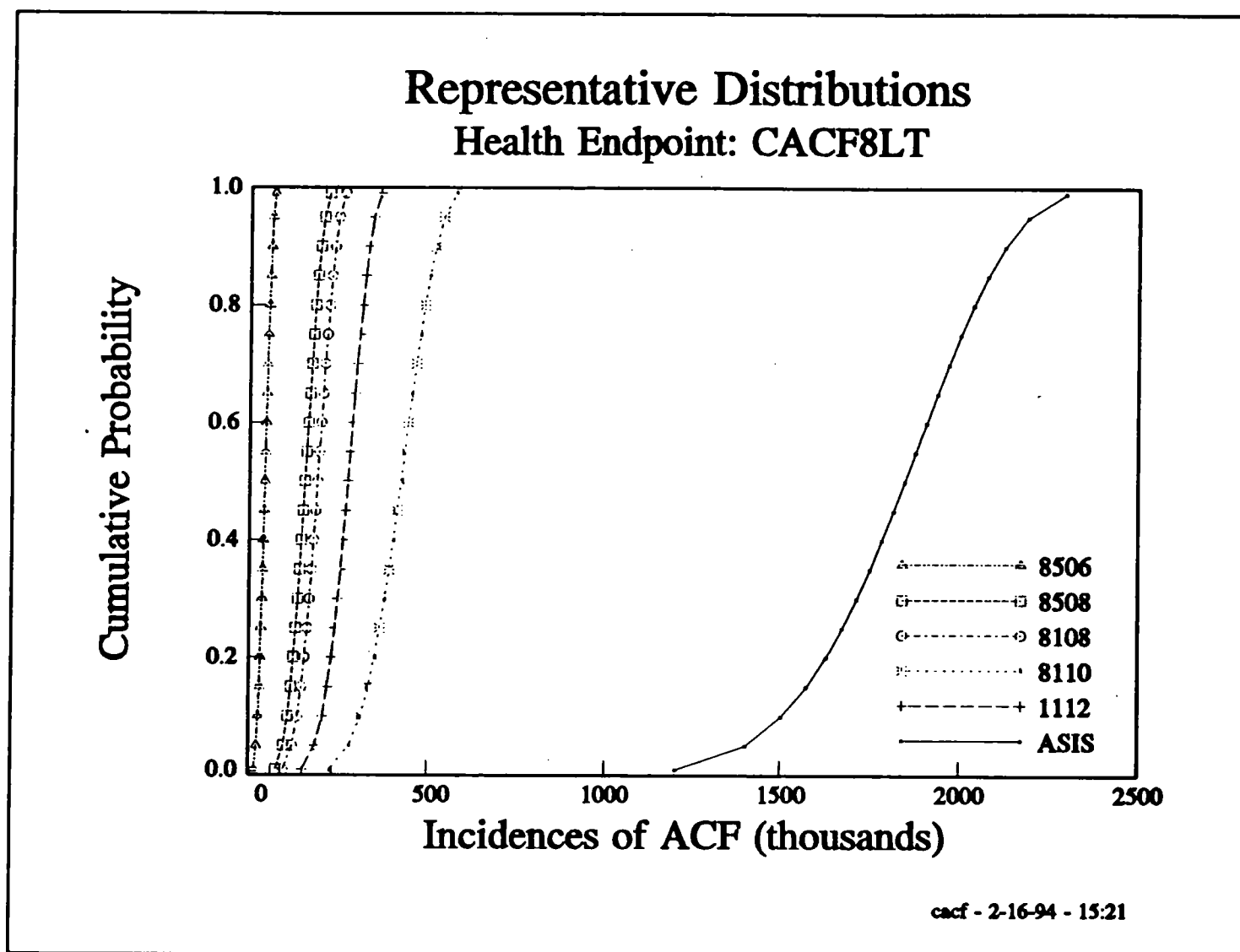


FIGURE A.27 Risk Distributions for Any Cough Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies (8-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

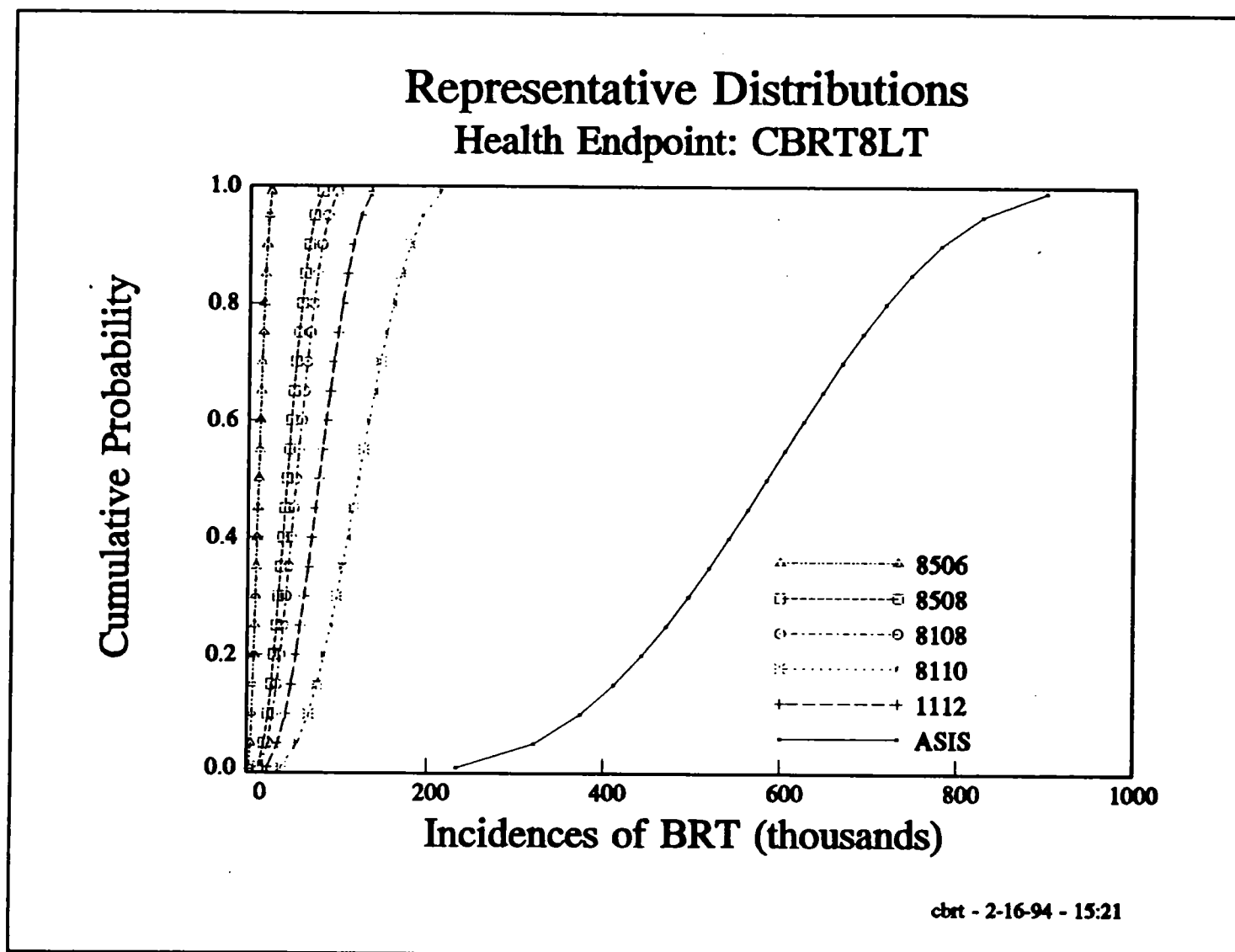


FIGURE A.28 Risk Distributions for Shortness of Breath Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies (8-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

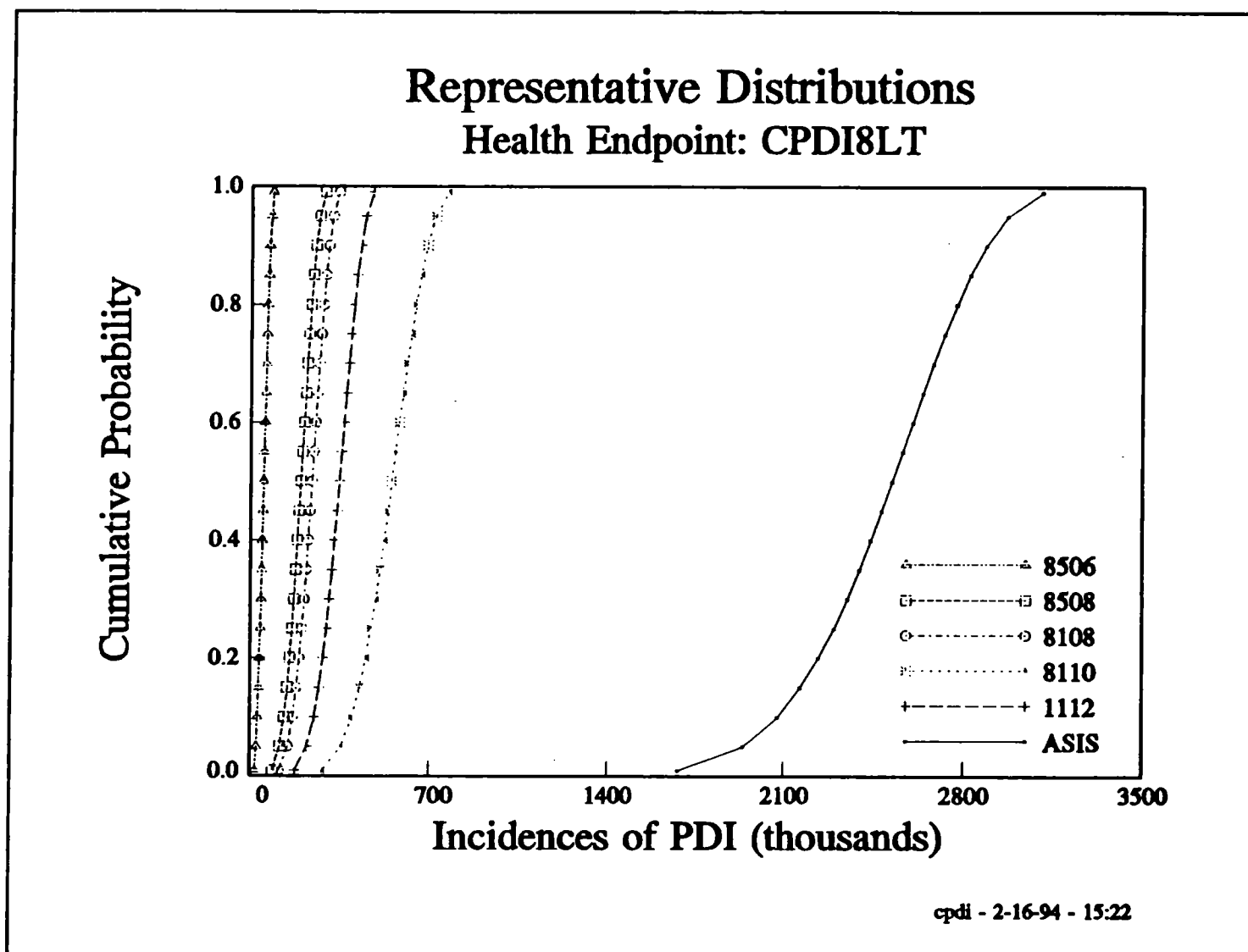


FIGURE A.29 Risk Distributions for Pain on Deep Inspiration Based on Data from the Folinsbee et al. (1988), Horstman et al. (1990), and McDonnell et al. (1991) Studies (8-hour exposures at moderate exercise, Los Angeles, total population, all air quality scenarios)

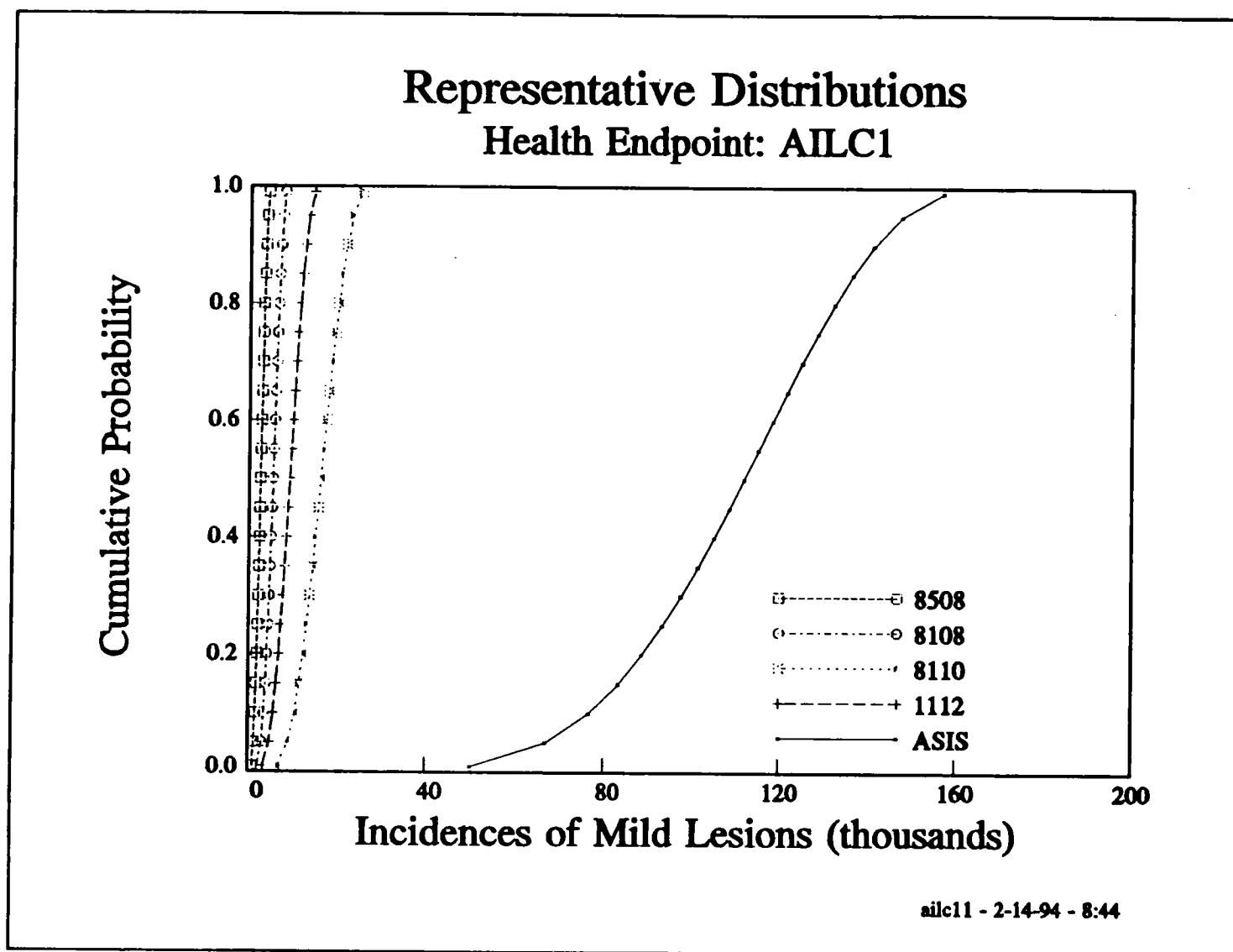


FIGURE A.30 Risk Distributions Expert A, Mild Lesions, Los Angeles, Children, 1 Season, All Air Quality Scenarios

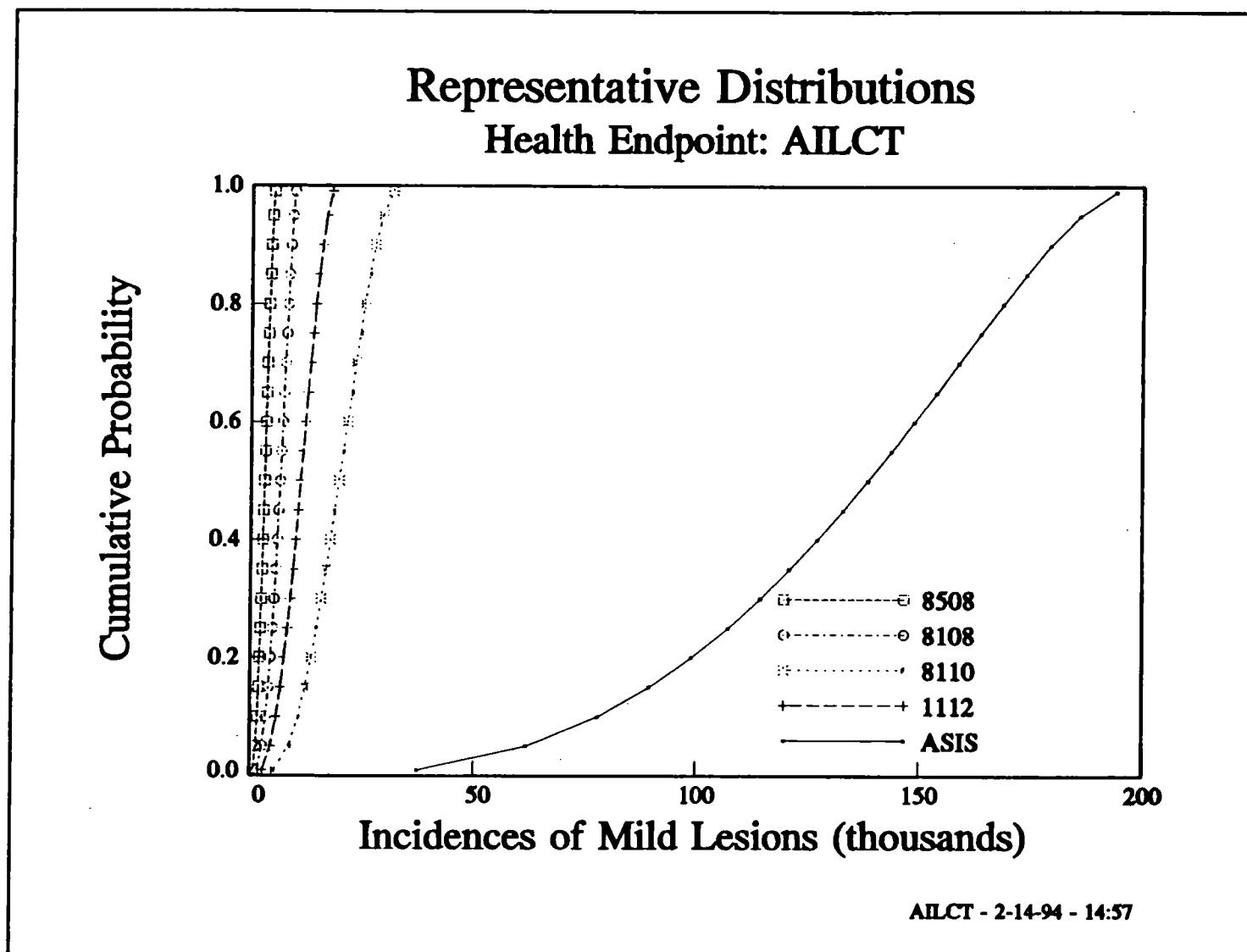


FIGURE A.31 Risk Distributions for Expert A, Mild Lesions, Los Angeles, Children, 10 Seasons, All Air Quality Scenarios

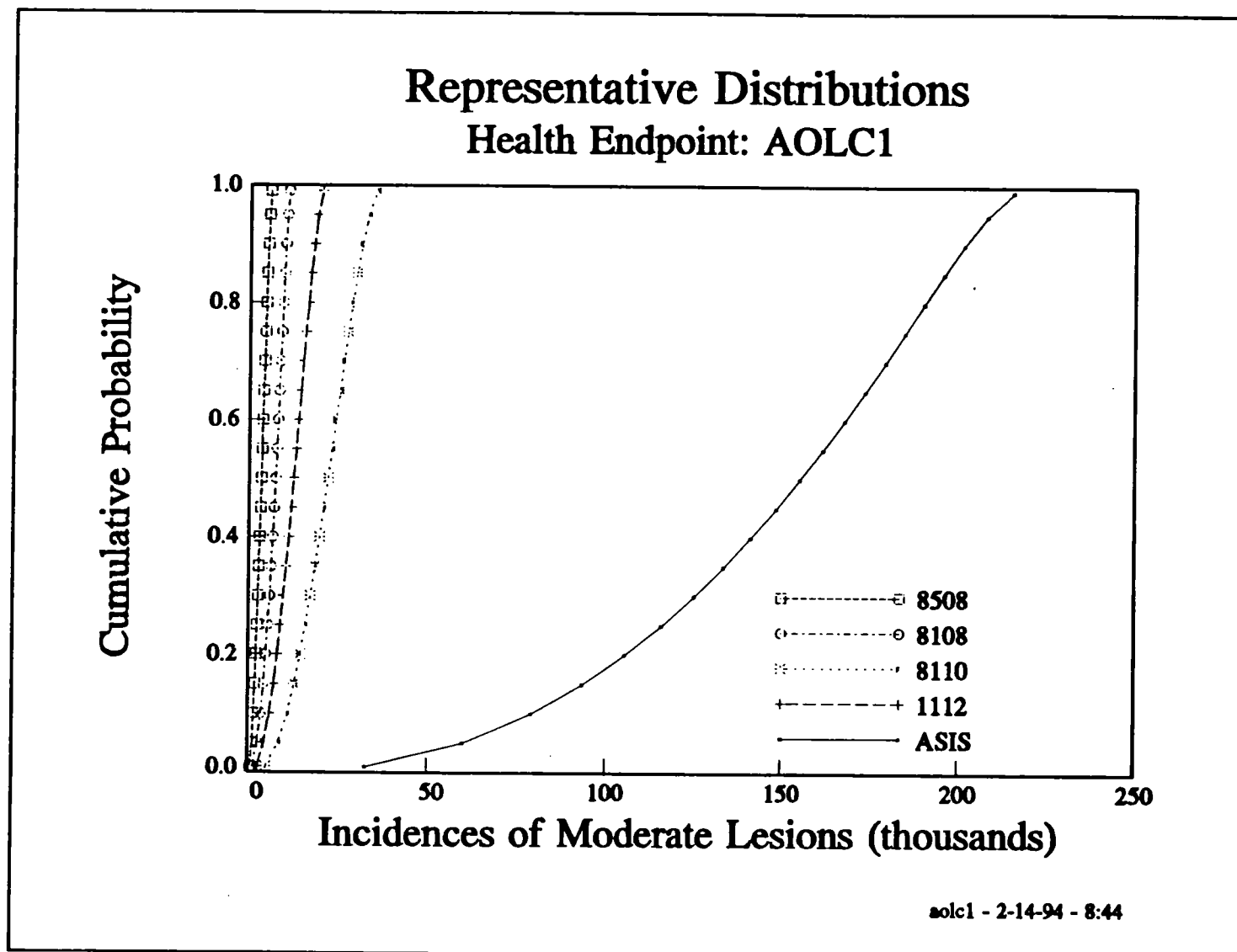


FIGURE A.32 Risk Distributions for Expert A, Moderate Lesions, Los Angeles, Children, 1 Season, All Air Quality Scenarios

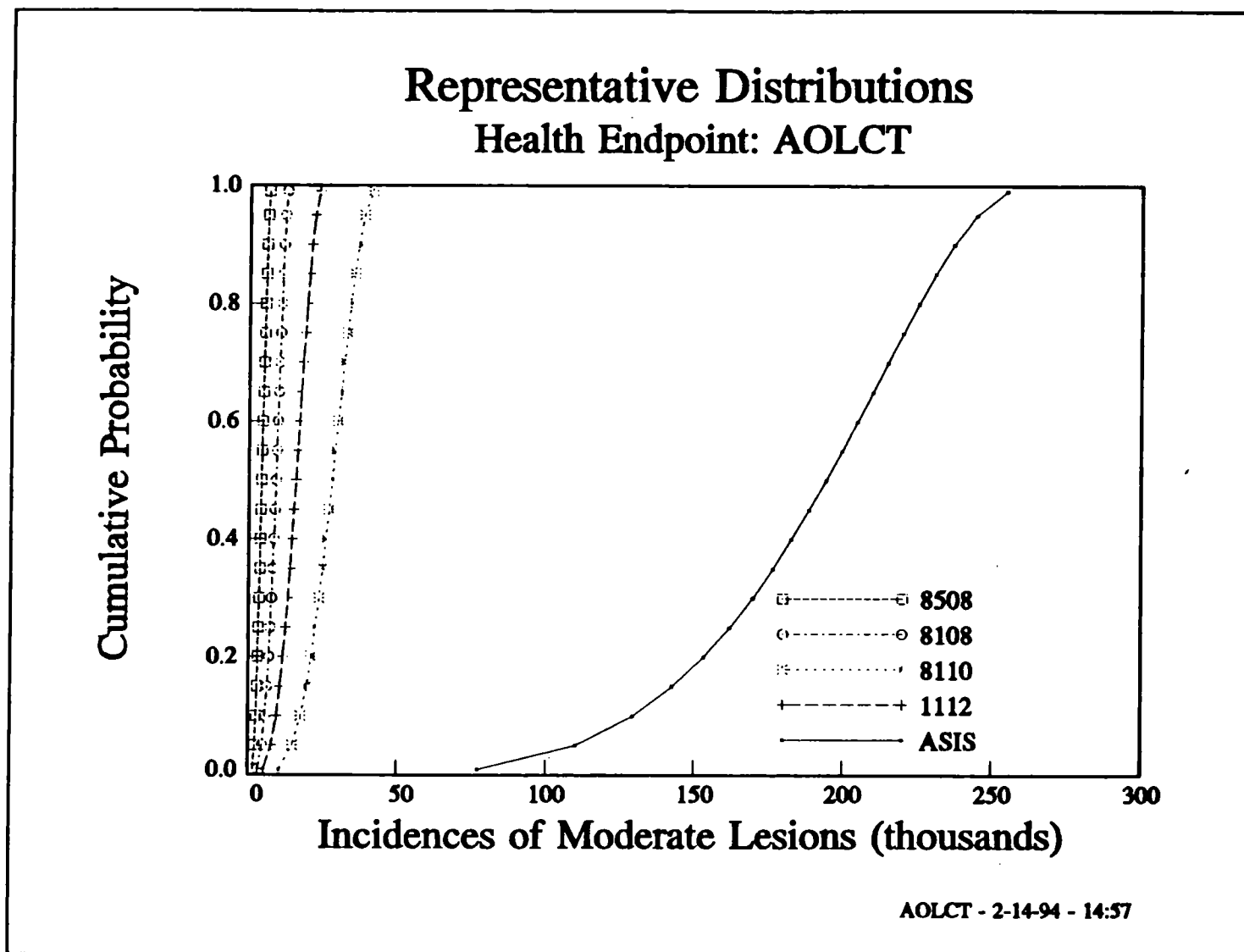


FIGURE A.33 Risk Distributions for Expert A, Moderate Lesions, Los Angeles, Children, 10 Seasons, All Air Quality Scenarios

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
RESEARCH TRIANGLE PARK, NC 27711

March 7, 1994

OFFICE OF
AIR QUALITY PLANNING
AND STANDARDS

Dr. George T. Wolff, Ph.D.
General Motors Corporation
Environmental & Energy Staff
Argonaut A-205-H
485 W. Milwaukee
Detroit, Michigan 48202-3220

Dear Dr. Wolff:

In reviewing the draft risk assessment methodology document I sent to you and the Clean Air Scientific Advisory Committee's (CASAC's) Subcommittee on Ozone (O₃) Exposure and Risk, I thought it might be useful for members of the Subcommittee to have some additional background material. Therefore, I am transmitting the enclosed materials directly to you and the Subcommittee members.

The document, Assessing the Risk of Chronic Lung Injury Attributable to Long-Term Ozone Exposure, dated July 1991, describes in detail how the chronic lung injury exposure-response relationships were obtained. The report was prepared by Argonne National Laboratory under an interagency agreement with the Environmental Protection Agency. As explained in the draft risk assessment methodology document, the Ambient Standards Branch proposes to use these exposure-response relationships in the current health risk assessment for the ozone standard review.

Sincerely,

A handwritten signature in dark ink, appearing to read "Karen M. Martin".

Karen M. Martin, Ph.D.
Chief

Ambient Standards Branch

Enclosure

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Assessing the Risk of Chronic Lung Injury Attributable to Long-Term Ozone Exposure

**Environmental Assessment and
Information Sciences Division
Argonne National Laboratory**



Operated by The University of Chicago,
under Contract W-31-109-Eng-38, for the

United States Department of Energy

Assessing the Risk of Chronic Lung Injury Attributable to Long-Term Ozone Exposure

by R.G. Whitfield, T.S. Wallsten,* R.L. Winkler,* H.M. Richmond,* S.R. Hayes,*
and A.S. Rosenbaum*

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July 1991

Work sponsored by United States Environmental Protection Agency,
Office of Air Quality Planning and Standards

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CONTENTS

ACRONYMS, INITIALISMS, AND ABBREVIATIONS	vi
ACKNOWLEDGMENTS	vii
ABSTRACT	1
1 INTRODUCTION	1
1.1 Report Organization	2
1.2 Motivation	3
1.3 Judgmental Probability Encoding	4
2 RISK ASSESSMENT PROCESS	5
2.1 Background Material and Analytical Support	5
2.2 Development of the Encoding Protocol	6
2.2.1 Introduction	7
2.2.2 Centriacinar Lesions	7
2.2.3 Exposure Conditions	7
2.2.4 Population at Risk	8
2.2.5 Factors to Consider	8
2.2.6 Health Significance	8
2.2.7 Factors to Keep in Mind When Making Probability Judgments	8
2.2.8 Session Two: Discussion of Judgments, Health Significance, and Research Needs	9
2.3 Experts	9
2.4 Encoding Process	9
2.4.1 Exposure-Response Uncertainties	9
2.4.2 First Round of Encodings	10
2.4.3 Chronic Risk Assessment Workshop	11
2.4.4 Second Round of Encodings	11
3 RESULTS	13
3.1 Quantitative Results	13
3.1.1 Probability Judgments	13
3.1.2 Exposure-Response Relationships	15
3.1.3 Comparisons across Experts	19
3.2 Qualitative Judgments	32
3.2.1 Definition of the Health Endpoint	32
3.2.2 Extrapolation from Animals to Humans	33
3.2.3 Stratification in the Population at Risk	34
3.2.4 Sequence and Time Scale of Effects	34
3.2.5 Degree of Repair	35
3.2.6 Interaction with Other Pollutants	35
3.2.7 Health Significance	36

CONTENTS (Cont'd)

4	SUMMARY AND CONCLUDING REMARKS	38
4.1	Risk Assessment Process	38
4.2	Results	39
4.2.1	Quantitative Results	39
4.2.2	Qualitative Results	40
4.3	Concluding Remarks	41
	REFERENCES	44
	APPENDIX A: Encoding Protocol	47
	APPENDIX B: Example of the Ozone Air Quality and Exposure Information Provided to the Experts	59
	APPENDIX C: Probability Judgments	65
	APPENDIX D: Qualitative Judgments	77

FIGURES

1	Cumulative Probability Distribution over Response Rate at a Personal Exposure Level of 0.025 ppm for Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season	14
2	Cumulative Probability Distributions over Response Rates at Personal Exposure Levels of 0.025, 0.050, 0.075, and 0.100 ppm for Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season	14
3	Median Exposure-Response Relationship for Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season	16
4	0.05-Fractile, Median, and 0.95-Fractile Exposure-Response Relationships for Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season	16
5	Median and 90% CI Judgments of Expert A for Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season	19
6	Median and 90% CI Judgments of Expert A	20
7	Median and 90% CI Judgments of Expert B	21

FIGURES (Cont'd)

8	Median and 90% CI Judgments of Expert C	22
9	Median and 90% CI Judgments of Expert D	23
10	Median and 90% CI Judgments of Expert E	24
11	Median and 90% CI Judgments of Expert F	25
12	Medians and 90% CIs for Judgments about Mild and Moderate Lesions, Children, Los Angeles, and 1 and 10 Ozone Seasons	26
13	Medians and 90% CIs for Judgments about Mild and Moderate Lesions, Outdoor Workers, Los Angeles, and 1 and 10 Ozone Seasons	27
14	Medians and 90% CIs for Judgments about Mild and Moderate Lesions, Children, New York, and 1 and 10 Ozone Seasons	28
15	Medians and 90% CIs for Judgments about Mild and Moderate Lesions, Outdoor Workers, New York, and 1 and 10 Ozone Seasons	29
B.1	Example of the Exposure Information Provided to the Experts	62

TABLES

1	Codes for Sets of Judgments that Were Obtained for Each Case	18
C.1	Encoded Judgments about Population Response Rates for Ozone-Induced Lesions in the Centriacinar Region of the Human Lung	68

ACRONYMS, INITIALISMS, AND ABBREVIATIONS

AIDS	autoimmune deficiency syndrome
CD	criteria document
CI	credible interval
CMSA	consolidated metropolitan statistical area
EPA	U.S. Environmental Protection Agency
NAAQS	national ambient air quality standard
OAQPS	Office of Air Quality Planning and Standards
PAQM	Personal Air Quality Model
ppm	parts per million

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The authors also appreciate the efforts of those at Argonne National Laboratory who were instrumental in preparing this report. Mary Warren greatly improved the format and language of the report as a result of her thorough editing. George Thiruvathukal and Raja Sarma wrote many of the computer programs used to calculate results. Bobbi Walker and Barbara Rogowski prepared the manuscript for publication; Nancy Clodi prepared earlier drafts. The computer-generated graphics are the work of Linda Haley.

ASSESSING THE RISK OF CHRONIC LUNG INJURY ATTRIBUTABLE TO LONG-TERM OZONE EXPOSURE

by

R.G. Whitfield, T.S. Wallsten, R.L. Winkler,
H.M. Richmond, S.R. Hayes, and A.S. Rosenbaum

ABSTRACT

The research described here is part of a larger risk assessment project sponsored by the U.S. Environmental Protection Agency. The purpose of this research is to characterize scientific judgment regarding the risk of chronic lung injury to children aged 8 through 16 and adult outdoor workers due to long-term ozone exposure in areas with patterns of exposure similar to those found in southern California and the Northeast. The qualitative and quantitative judgments resulting from the work will not be used in the ongoing review of the ozone primary ambient air quality standard. They will instead be used to inform policymakers and the public about the possible health implications of long-term exposure to ozone. Our measure of injury is the incidence of mild or moderate lesions in the centriacinar region of the lung. The probabilities over population response rates were elicited from six health experts actively researching ozone-induced lung injury. We describe our approach and present the results in the form of judgmental probability distributions and associated qualitative comments over the population response rates for formation of lesions induced by exposure to ozone.

1 INTRODUCTION

This report summarizes the first phase of an assessment of the chronic health risks associated with long-term exposure to ozone. Ozone is a highly reactive irritant gas that is present in elevated amounts throughout much of the United States. The U.S. Environmental Protection Agency (EPA) estimates that in 1988 about 120 million people lived in counties in which the current one-hour ozone national ambient air quality standard (NAAQS) of 0.12 parts per million (ppm) was exceeded. This ozone concentration is not to be exceeded on average on more than one day per year.

The Clean Air Act charges EPA with setting, reviewing, and revising, as appropriate, the primary NAAQS for selected pollutants. The primary standards, which are to be set at levels sufficient to protect public health with an adequate margin of safety, are based on scientific evidence presented and reviewed in "criteria documents" (CDs). In support of the current review of the ozone NAAQS, EPA has prepared a new CD entitled *Air Quality Criteria for Ozone and Other Photochemical Oxidants* (EPA, 1986), a CD Supplement (EPA, 1988), and an Office of Air Quality Planning and Standards (OAQPS) Staff Paper (EPA, 1989). The CD and CD Supplement summarize and evaluate the human clinical, epidemiological, and animal toxicological evidence regarding the physiological and adverse health effects resulting from exposure to ozone and

other photochemical oxidants. These documents present current knowledge about the health effects associated with exposure to ozone as found in the peer-reviewed scientific literature published through December 1988. In the OAQPS Staff Paper, the material presented in the CD and CD Supplement is interpreted and recommendations are made to the EPA Administrator.

During the current review of the ozone NAAQS, the issue has been raised as to whether repeated or long-term exposure to ozone at levels observed in areas such as southern California and the Northeast leads to chronic effects in the form of irreversible lung injury or lung disease. The results of the animal toxicology studies discussed in Chapter 10 of the CD suggest that ozone exposure at sufficiently high concentrations over a prolonged enough period results in permanent structural changes to the lung. Among the possible effects of prolonged exposure are narrowing of the distal airways (i.e., thickened respiratory bronchiole walls), remodeling of the centriacinar airways, and thickening of the interalveolar septa resulting in part from increased collagen and epithelial thickening.

For the assessment described in this report, EPA chose mild and moderate lesions in the centriacinar region of the lung as the health endpoint for which judgments about probabilistic exposure-response relationships were to be elicited. The centriacinar region of the lung has been shown to be the location of maximum ozone dose and maximum lung injury in a number of species (i.e., rats, guinea pigs, and monkeys) exposed to elevated ozone concentrations (EPA, 1986). The health scientists consulted in the early phases of this assessment agreed that centriacinar lesions are a good indicator of potential chronic lung injury caused by ozone exposure. For this assessment, EPA selected children aged 6 through 18 and all adult outdoor workers in two urban areas – New York City and Los Angeles – as the populations of interest. These two groups were thought to be at greater risk for chronic effects because their members tend to be outdoors more than most individuals when ozone concentrations are at their highest.

The purpose of the assessment described in this report is to better characterize scientific judgment regarding the risk of lung injury or disease due to long-term ozone exposure. The qualitative and quantitative results of this assessment are being used to inform policymakers and the public about the possible health implications of long-term exposure to elevated levels of ozone as judged by scientists very familiar with research on the health effects of ozone. They are not being used in the ongoing review of the ozone primary NAAQS. However, this assessment provides valuable lessons for risk assessments that may be conducted during the next round of review of the ozone NAAQS. Finally, this assessment provides new insight into the opinions of the scientific research community about the research needed to reduce uncertainties about the chronic health effects associated with exposure to ozone at elevated levels.

1.1 REPORT ORGANIZATION

To the extent possible, the details of the assessment are presented in appendixes. Nevertheless, readers can gain a good understanding of the results from the main text. Section 1.2 presents the reasons for choosing the particular form of the risk assessment; Section 1.3 discusses the role of judgmental encoding in the risk assessments.

Section 2 presents the procedure used for the risk assessment. The procedure included developing an assessment protocol and encoding the judgments of six health experts. Section 3.1 provides the details of the encoding process and the development of probabilistic dose-response relationships by focusing on the judgments of one of the experts and on summaries and

comparisons of the judgments of all the experts. The qualitative judgments recorded are summarized in Section 3.2. Section 4 summarizes the main findings and provides concluding remarks. Appendix A contains the encoding protocol; Appendix B gives examples of the ozone air quality and exposure information provided to the health experts; Appendix C lists their probability judgments; and Appendix D summarizes their qualitative judgments.

1.2 MOTIVATION

Assessing the health risks for children and adult outdoor workers exposed to ozone requires assessing the probabilities of certain fractions of these populations suffering well-defined health effects under alternative exposure scenarios. The probabilities must be assessed in a formal, defensible manner that is open to public scrutiny. They will generally reflect two sources of uncertainty, that is, one deriving from the characteristics of the data and the other from a lack of knowledge. The former type of uncertainty reflects measurement and sampling error, and probabilities are generally calculated by means of standard procedures. Although this type of uncertainty can be reduced through experimental manipulation, it cannot be eliminated completely in any finite study.

The latter type of uncertainty reflects the paucity, incompleteness, and indirect nature of much of the available data. For example, it is frequently necessary to make inferences about a health effect in a specified population on the basis of epidemiological or clinical data on different populations under varying or different exposure conditions, or on the basis of laboratory data on other species or on in vitro preparations. Statistical techniques cannot quantify this type of uncertainty because it is judgmental in nature. Uncertainty can, however, be quantified by using appropriate procedures to encode judgmental probabilities. Experts will assess the uncertainty differently, depending on their faith in the implicit or explicit theories underlying their extrapolations from the data to the effect in question and on their perception of the distance over which the extrapolation must be made. Therefore, the procedures must be able to accommodate and represent a possible divergence in the judgments. The degree of this type of uncertainty, as well as the degree of divergence among experts, can be reduced.

Conducting a risk assessment in which these two types of uncertainty are accommodated responds well to a challenge issued by former EPA Administrator William Ruckelshaus in a speech at Princeton University (Ruckelshaus, 1984, p. 158):

... If I am going to propose controls that may have serious economic and social effects, I need to have some idea of how much confidence should be placed in the estimates of risk that prompted those controls.

In the same talk, he went on to propose some principles for reasonable discussion about risk (p. 161):

First, we must insist on risk calculations being expressed as distributions of estimates and not as magic numbers that can be manipulated without regard to what they really mean. We must try to display more realistic estimates of risk to show a range of probabilities. To help do this we need new tools for quantifying and ordering sources of uncertainty and for putting them in

*Section 1.2 is adapted from Section 1.2 in Wallsten and Whitfield (1986).

perspective. Second, we must expose to public scrutiny the assumptions that underl[ie] our analysis in management of risk.

Generally, the information relevant to a particular health effect associated with an environmental agent will be indirect and incomplete, and experts will differ as to the associated judgmental uncertainty. The degree of agreement among the experts will be a measure of the firmness of the probability estimates. This information will be useful to policymakers and the public.

The sessions with each health expert to encode probabilities can include discussions about the relevant data. These discussions supplement the probability distributions and provide guidance on their use. This report presents the probability judgments elicited from the experts and summaries of the associated discussions.

1.3 JUDGMENTAL PROBABILITY ENCODING*

Judgmental probability encoding is unnecessary if adequate direct data are available. However, more often than not, such data are unavailable, and the only alternatives to encoding judgmental probabilities are to treat the added uncertainty qualitatively, which currently cannot be done in a rigorous manner, or to ignore it altogether, which is indefensible.

For encoded judgmental probabilities to be useful, they must satisfy two important criteria. The first criterion is that judgments must be obtained from a limited number of experts who span the range of respected opinion. The problem of establishing the range of respected opinion and selecting appropriate experts is difficult and judgmental in nature; however, the relevant issues tend to be debated frequently and publicly enough that such decisions are possible. For this assessment, EPA's OAQPS, with assistance from the Environmental Criteria and Assessment Office, selected the experts whose judgments were to be encoded. Although their names are given in Section 2.3, their individual judgments and discussion summaries are identified by code letter only. In this way, users of the risk assessment results can decide whether the full range of opinion is represented, and the individual experts could respond freely without worrying that they might become involved in endless arguments or discussions with those who might disagree.

The second criterion is that an individual's encoded probability judgments must be stable (barring new information), must be coherent in a well-defined way, and must accurately represent his or her uncertainty. Research relating to these issues has been reviewed by Wallsten and Budescu (1983), and an experiment specifically addressing them in a context similar to the research described here was performed by Wallsten and Budescu (1983). The techniques used in this assessment are based on this foundation but also rely on previous health risk assessments for lead (Wallsten and Whitfield, 1986; Whitfield and Wallsten, 1989).

*Section 1.3 is adapted from Section 1.3 in Wallsten and Whitfield (1986).

2 RISK ASSESSMENT PROCESS

If scientific judgments regarding the risk of lung injury due to long-term ozone exposure are to be assessed accurately, a carefully designed protocol is necessary. Thus, after appropriate background material and supporting information were compiled, a protocol for encoding the judgments of experts (Appendix A) was developed. The protocol was then pilot-tested and modified and the experts to be interviewed chosen. Initially, two or three members of the risk assessment team met with each expert individually to encode his or her judgments. Feedback was later provided to the experts. Next, the risk assessment team and the experts met to discuss the quantitative risk assessments and the underlying qualitative factors. After the workshop, members of the risk assessment team again met with each individual to finalize his or her probability judgments. This process is described in this section, and the results are summarized and discussed in Section 3.

2.1 BACKGROUND MATERIAL AND ANALYTICAL SUPPORT

The background material needed for the encoding process is contained in the EPA CD for ozone (EPA, 1986), the CD Supplement (EPA, 1988), and the OAQPS Staff Paper (EPA, 1989) mentioned in Section 1. The first two documents summarize the scientific evidence regarding the adverse health effects associated with ozone exposure, while the third discusses the implications of that evidence. These materials aided in defining the health endpoints of interest and identifying the factors that may affect them. Moreover, they provided a convenient summary for the experts as they reviewed the relevant evidence on the adverse health effects of ozone.

Because most of the available evidence concerning chronic effects of ozone exposure is based on animal studies, differences between animals and humans must be considered in making judgments about chronic effects in humans. To provide information that might be helpful in this extrapolation process, an ozone dosimetry model was run to simulate lower respiratory tract doses for various combinations of activity patterns and exposure concentrations in rats, children, and adults. The combinations selected fit the populations and exposure concentrations to be used in the encoding process. Features of the ozone dosimetry model are described in Miller et al. (1985), Overton, Graham, and Miller (1987), and Overton et al. (1990). Enhancements for this simulation included modification of the model to represent the upper respiratory tract and modification of some parameters to reflect recent experimental results. The results of the dosimetry simulation were summarized for the experts in figures showing, for different combinations of conditions: (1) predictions of cumulative respiratory tract net ozone doses by airway generation* for a 12-hour period, (2) ratios of selected pairs of these predictions, and (3) centriacinar region net doses for a sequence of 1-hour periods for each of the 12 hours.

After much consideration of the best way to specify exposure patterns for the purpose of obtaining judgments about dose-response functions, we decided to specify them in terms of seasonal mean daily maximum eight-hour average concentrations of personal exposure. Of course, for a given seasonal mean daily maximum eight-hour average, there is considerable

*Each successive branching of airways in the lung is called a generation. For example, the trachea is generation 0, bronchi are generation 1, etc.

variability in the daily eight-hour averages within an ozone season and even from hour to hour within a given day.

To help the experts think about the variability in exposure associated with a given mean, personal exposure patterns were simulated for the populations in the locations of interest. We used the Personal Air Quality Model (PAQM) (Hayes, 1989), which simulates indoor and outdoor exposure by taking into account individual hourly activity profiles. The activity profiles were based on diary data provided by individuals representative of the target populations (Roddin, Ellis, and Siddiquee, 1979). Ambient concentrations of ozone were obtained from "design" monitor data and adjusted to yield, when combined with the activity patterns, different personal seasonal mean daily maximum eight-hour averages. Results were presented in the form of histograms for each of four such seasonal daily maximum eight-hour personal means. For each mean, the first histogram displayed the distribution of daily maximum eight-hour average personal exposures; the second showed the distribution of daily maximum hourly personal exposures; and the third showed the distribution of ambient daily maximum concentrations. Separate sets of histograms were developed for each population-location of interest. We also provided other information, such as data on seasonal variation in ozone level or on distributions of respites between peaks above certain levels. These figures, along with a brief description of how they were generated, were provided to the experts prior to the encoding sessions. Examples of this material are given in Appendix B. The full results and a complete description of the procedures are presented in Rosenbaum and Hayes (1990).

By presenting such detailed and realistic measures of the variability associated with a given seasonal mean daily maximum eight-hour average concentration of personal exposure, it was possible to elicit the judgments of the experts about population response rates at certain mean values without depriving them of potentially relevant information. For example, an expert who believed that peak rather than cumulative exposures were damaging could consult the distribution of peak values for the specified mean.

2.2 DEVELOPMENT OF THE ENCODING PROTOCOL

A carefully developed encoding protocol was crucial to the success of the project. It ensured that the questions for the experts were always phrased identically, that specific assumptions and definitions were always the same, and that the encoding process proceeded similarly for each of the participants. Consequently, the differences in probability judgments could be attributed to true differences of opinion and not to differences in assumptions, understandings, or procedures.

In developing the encoding protocol, we drew heavily on the assembled background material and consulted extensively with individuals (named in the acknowledgments) having expertise in different aspects of the problem. Of particular concern were the appropriate health endpoints to consider and the best way to represent exposure conditions. However, many other points also required careful attention. Dealing with chronic rather than acute effects greatly increased the number of factors that had to be considered.

On the basis of the literature and discussions with consultants, we prepared a draft of the encoding protocol. At various points, the draft was circulated to some or all of the participating consultants. Written comments were received in some cases; meetings were held in others. In this manner, several drafts of the protocol were generated and revised.

After several revisions, the protocol was pilot-tested on an EPA staff member and an EPA contractor. Some weaknesses not previously recognized became apparent during the pilot testing, and the protocol was revised further to correct them. Consultations and discussions among members of the risk assessment team led to some final fine-tuning to create the protocol that was actually used in the encoding process. A copy of this protocol is presented in Appendix A. In the remainder of this section, each part of the protocol is briefly discussed. The focus of these discussions is on the role played by that particular part of the protocol and on questions that arose during its development.

2.2.1 Introduction

This section of the protocol presents the motivation for and objectives of the encoding process.

2.2.2 Centriacinar Lesions

In this part of the protocol, the health endpoints of interest are defined as mild and moderate centriacinar lesions. The results of animal studies suggest that long-term ozone exposure can lead to numerous structural changes in the lung, such as narrowing of distal airways, remodeling of the centriacinar airways, and thickening of the interalveolar septa. Each of these health effects is important, and all are correlated. However, it is only when one of them is precisely defined that the concept of a dose-response function can be applied to it. Even then, it is not always clear what level of the endpoint should be considered adverse. It was therefore necessary for the encoding process to select an endpoint for which mild and moderate levels could be precisely defined. The mild level was at the lower end of what might be considered adverse, and the moderate level was somewhat farther along on the continuum.

After much consultation, we decided to focus on centriacinar lesions, with the two levels defined in terms of the techniques required to detect them. In the protocol, mild centriacinar lesions are defined as "those detectable only by highly sensitive techniques and quantitative analysis" (e.g., morphometric techniques, special stains, and electron microscopy). Moderate centriacinar lesions are defined as "those detectable by qualitative assessment using light microscopy but not necessarily gross techniques." The need for and importance of extrapolation from animal results to humans are emphasized in this section.

2.2.3 Exposure Conditions

To deal with chronic effects, we decided to consider centriacinar damage over a single ozone season and also over 10 ozone seasons. Specifying exposure conditions within a season required extensive consultation because of variations in exposure pattern over time. Ambient ozone concentrations vary diurnally, over days, and throughout the season. Moreover, an individual's personal exposure depends on his or her location and activity level at any point in time. The challenge was to represent typical exposure variations within a season in an easily comprehensible manner while specifying exposure levels in a form suitable for discussing dose-response functions. This task was particularly important because experts differ as to the ozone exposure characteristics they deem instrumental in causing adverse health effects. We did not want to omit or misrepresent exposure information that might be deemed crucial.

Our solution was to specify seasonal mean daily maximum eight-hour exposure values for individuals of 0.025, 0.050, 0.075, and 0.100 ppm. For each seasonal mean and for each of two populations in two geographic locations, we provided associated data on the distributions of these personal exposures, on the distributions of personal and ambient daily peak exposures, and on other characteristics of the exposure patterns. As described in Section 2.1, these data were derived to be as representative as possible of the actual range of conditions associated with a given seasonal mean value for each population of interest in each geographic location. The histograms (discussed in Section 2.1) illustrating patterns of exposure are explained in this part of the protocol, as are the dosimetry results. The assumptions made regarding exposure history, ambient conditions, and other air pollutants are also stated.

2.2.4 Population at Risk

The populations considered for the encoding are all children aged 6 through 18 and all adult outdoor workers in Los Angeles and New York City. These populations include people with and without respiratory problems and allergies, smokers and nonsmokers, and people exhibiting different levels of activity. We decided not to stratify our populations along any of these dimensions, although we did not rule out the possibility that one or more experts might wish to do so. (As it turned out, none did.) Therefore, the experts had to assume distributions for these and any other factors that they believed to exist in the populations of interest.

2.2.5 Factors to Consider

This part of the protocol serves to remind the experts of factors that may be relevant to their judgments: results reported in the literature, issues concerning extrapolation from animal studies, stages of response, time scales of effects, levels of repair, effects of varying the exposure concentrations over time (e.g., relative importance of cumulative exposure versus peak exposure), and possible interactions of ozone with other air pollutants. The experts are asked about their qualitative judgments concerning these factors.

2.2.6 Health Significance

This brief part of the protocol simply sets the stage for an exploration of the experts' opinions about the long- and short-term health consequences of lung damage resulting from long-term ozone exposure. Important questions include how significant the centriacinar lesions are in themselves and what implications they might have for a person's future health.

2.2.7 Factors to Keep in Mind When Making Probability Judgments

The purpose of this part of the protocol is to help the experts provide probabilities that accurately represent their judgments. This objective is accomplished primarily through review of some commonly found cognitive biases and simplifying heuristics and through some suggestions on how to try to mitigate their effects. This material is not unique to this protocol, having been used in previous risk assessment protocols. The topics covered include (1) effects related to the order in which evidence is considered or probabilities assessed, (2) the effect of memory on judgment, (3) the tendency to overestimate the reliability of information, (4) the influence of

the importance of events on probability judgments, and (5) the difficulty of discriminating between levels of uncertainty.

2.2.8 Session Two: Discussion of Judgments, Health Significance, and Research Needs

This part of the protocol simply notes the plan for a meeting at which the experts are to exchange judgments, both quantitative and qualitative.

2.3 EXPERTS

The judgments of the following experts were encoded:

Dr. Daniel Costa - U.S. Environmental Protection Agency
Dr. James Crapo - Duke University
Dr. Charles Plopper - University of California, Davis
Dr. Russell L. Sherwin - University of Southern California
Dr. Walter Tyler - University of California, Davis
Dr. Elaine Wright - General Motors Corporation

The experts were chosen on the basis of their knowledge and familiarity with the health effects of ozone exposure as well as their various viewpoints and approaches. The experts were not, and should not have been, chosen randomly. Rather, they were selected for their expertise and because, as a group, they represent the range of respected scientific opinion on the questions of interest.

2.4 ENCODING PROCESS

2.4.1 Exposure-Response Uncertainties

The probability judgments of the experts regarding 16 exposure-response functions under particular exposure conditions were encoded. The functions represented all possible combinations of severity of lesions (mild or moderate), location (Los Angeles or New York), population (child or adult outdoor worker), and number of seasons of ozone exposure (1 or 10). The encoded probabilities were to represent each expert's best judgment regarding what the population response rate (i.e., proportion of the population showing the adverse health effect) would be at each of four ozone levels (i.e., seasonal mean daily maximum eight-hour averages of 0.025, 0.050, 0.075, and 0.100 ppm) under the specified conditions.

Specifically, for a given function and exposure level, the expert was to judge the chances of various response rates occurring, taking into consideration the exposure pattern and all other relevant factors. By means of a series of questions to be described in Section 2.4.2, these judgments were translated into a probability distribution over a response rate. Thus, for each expert and each exposure-response function, four probability distributions over the population response rate were encoded, one at each exposure level.

2.4.2 First Round of Encodings

For the first round of encodings, each of the six experts was visited by two or three members of the risk assessment team. One pair from the team encoded the judgments of three of the experts, and three other team members encoded those of the remaining experts. The time required for these encoding sessions ranged from half a day to a full day. The experts were visited between July 26, 1989, and August 30, 1989.

The basic structure of the six encoding sessions was the same. The experts had received the background material, the dosimetry results, the exposure results, and the protocol prior to the meeting and had been asked to look over these materials. The encoding session began by going through the protocol with the expert and making sure he or she understood the definitions and assumptions. During this review, questions were asked and qualitative judgments obtained about various aspects of the chronic health effects of ozone exposure, with particular emphasis on the factors to consider and the health consequences. This format encouraged the expert to think about issues highly relevant to the later encoding of probability judgments and also provided valuable qualitative information. Attention was also paid to the dosimetry results and the exposure results. This part of the session lasted from two to four hours.

Probability judgments were then obtained for 16 exposure-response functions (Section 2.4.1). These functions were considered in pseudo-random order. For each one, the four mean daily maximum eight-hour average concentrations were considered, also in pseudo-random order. For each function and each mean exposure level, the expert's probability distribution for response rate (i.e., percentage of the population developing ozone-induced lesions) was obtained.

Typically, the probability encoding process started slowly and then moved along more quickly as the expert became more comfortable with the encoding process and with the notion of expressing judgments in probabilistic form. To help the expert understand the questions, they were phrased in more than one way (e.g., probabilities versus odds and probability above versus below a given value). A probability wheel was used as an aid. The wheel is divided into two radial and adjustable segments of different colors. One of the two colors is adjacent to a pointer. The proportion of the wheel's area devoted to one color can be varied continuously from zero to one. For example, the expert was asked, for a given wheel setting, which is more likely: (1) the wheel, if spun, will stop with the pointer on blue, or (2) less than 30% of the population will develop mild lesions at a certain mean exposure level. The relative proportions of the two colors on the wheel are adjusted until the expert can no longer judge either (1) or (2) as more likely. Most of the six experts relied heavily on the wheel; several preferred to simply state their probabilities.

For each function and each mean exposure level, probabilities for several response rates were encoded. After this was done for all four mean exposure levels for a given case, the probabilities were plotted on a graph and shown to the expert. Any inconsistencies were pointed out. For example, there might have been a higher probability for a given response rate at a lower exposure level than at a higher exposure level. Actually, few such inconsistencies were encountered. At this juncture, we pointed out the implications of the probabilities and asked the expert (regardless of whether there had been any inconsistencies) if the set of probabilities adequately represented his or her judgments. Changes were made, if necessary. Throughout the process, the experts were encouraged to reconsider earlier probability judgments and to change them if they no longer seemed appropriate.

The experts sometimes went through the entire encoding procedure for each new function. However, they sometimes simply used their judgments from a previous case. For example, an expert might judge that the probabilities should be the same for outdoor workers in New York and Los Angeles. In other cases, they simply adjusted previously encoded probabilities from a related function.

When encoding was completed for all cases, the expert was once again offered the opportunity to reconsider his or her judgments. Each expert was then told that further opportunities for modifications would be available when the judgments were sent to the expert and later when the second round of encoding took place.

2.4.3 Chronic Risk Assessment Workshop

On September 16, 1989, the six experts, the risk assessment team, and EPA staff members met for a workshop chaired by Dr. Judy Graham. The entire day was devoted to discussions of qualitative and quantitative judgments regarding chronic health effects of long-term exposure to ozone. Workshop participants again went over the issues covered in the protocol and discussed during the first round of encodings. The interactions among the experts added new elements to the picture.

Discussions of the qualitative judgments covered the following topics: definition of health endpoints, nature and significance of health effects, definition of exposure scenarios, dosimetry modeling, sequence of response, time scale of effects, effect of varying concentrations over time, degree and role of repair, interaction with other air pollutants, and discriminatory variables for encoding. The role of the risk assessment team and EPA staff was to facilitate the discussion. The experts did most of the talking, with all six experts actively participating. Positions were stated and debated, and relevant research too new to be widely available was introduced. There was considerable give and take among the experts.

After the qualitative discussions, the experts were given feedback regarding the probability judgments made during the first round of encoding. They were shown the probability judgments of all six experts, but anonymity was maintained. In the presentation, the experts were labeled A, B, C, D, E, and F, and not by name. Each knew only his or her code letter. A general discussion of the probability judgments ensued, with some emphasis on differences among experts. A discussion of important research needs followed.

At the end of the afternoon session, the experts were asked to give their reactions to the workshop itself. They were unanimous in stating that it had been very informative and valuable. One expert claimed that the encoding process and workshop had led to an entirely new way to think about research and the adverse effects associated with exposure to ozone.

2.4.4 Second Round of Encodings

The following morning, the second round of encodings took place, with five of the six experts participating. The sixth expert was unavailable that day but subsequently went through the same process. In the second round, members of the risk assessment team met with the experts individually. The probability judgments encoded during the first round were reviewed. The experts were asked to reconsider their judgments in light of what had happened at the

workshop. It was emphasized that the intent was to obtain their current judgments and not to force consensus. These sessions proceeded quickly, lasting from one to four hours.

3 RESULTS

This section presents both quantitative and qualitative results. The quantitative results are the judgments of experts about the probability of occurrence of ozone-induced lesions in the centriacinar region of the human lung. These results are presented graphically in two ways: (1) probability distributions over response rate (conditional on exposure level and other factors) and (2) exposure-response relationships. Initially, the judgments of Expert A are presented for illustrative purposes; the judgments of all the experts are then displayed graphically. The qualitative results include explanations for and implications of the judgments made and discussions held at the encoding sessions and workshop.

3.1 QUANTITATIVE RESULTS

3.1.1 Probability Judgments

Judgments were obtained from the six experts about the probability of occurrence of ozone-induced lesions in the centriacinar region of the lung. Probability encoding techniques were used to obtain these judgments in the form of probability distributions over response rate (conditional on exposure level and other factors). Other factors included population (child or adult outdoor worker), geographic area (Los Angeles or New York), number of exposure seasons (1 or 10), and degree of lesion (mild or moderate).

For example, Figure 1 shows the conditional probability distribution over response rate obtained from Expert A for the occurrence of mild lesions in the centriacinar region of the lung among children living in Los Angeles exposed for one season to ozone concentrations with a mean daily maximum eight-hour average of 0.025 ppm at the mouth. Probabilities were elicited from Expert A for eight possible response rates at the mean concentration of 0.025 ppm under the specified conditions. Adjacent points are connected by straight lines. The set of points and straight lines is referred to as a curve. In Expert A's judgment, the possible response rate varies from 0.15 (with cumulative probability 0.01) to 0.75 (with cumulative probability 0.99). The median response rate (i.e., the rate associated with cumulative probability 0.5) is 0.35. The 0.15 and 0.75 response rates constitute Expert A's 98% credible interval (CI), an interval that (in Expert A's judgment) includes the "true" response rate with probability 0.98. In other words, Expert A believes there is a 50-50 chance that less than 35% of the population will develop ozone-induced lesions for this exposure regimen. Expert A also judges the probability to be 0.98 that between 15% and 75% of the population will experience the effect.

Probability judgments were also elicited from Expert A at mean ozone concentrations of 0.050, 0.075, and 0.100 ppm for the specified conditions. These judgments and those for 0.025 ppm are compiled in Figure 2. Each of the four curves is a set of points connected by straight lines. To help distinguish between the curves, different symbols are used to represent the encoded points on each curve, and different styles are used for the line segments that connect adjacent points. Note that the curves do not intersect and that they are monotonic increasing. This monotonic-increasing property is a necessary condition for a function to be a

*Some of these results are reported in Winkler et al. (1990) and Wallsten et al. (1990).

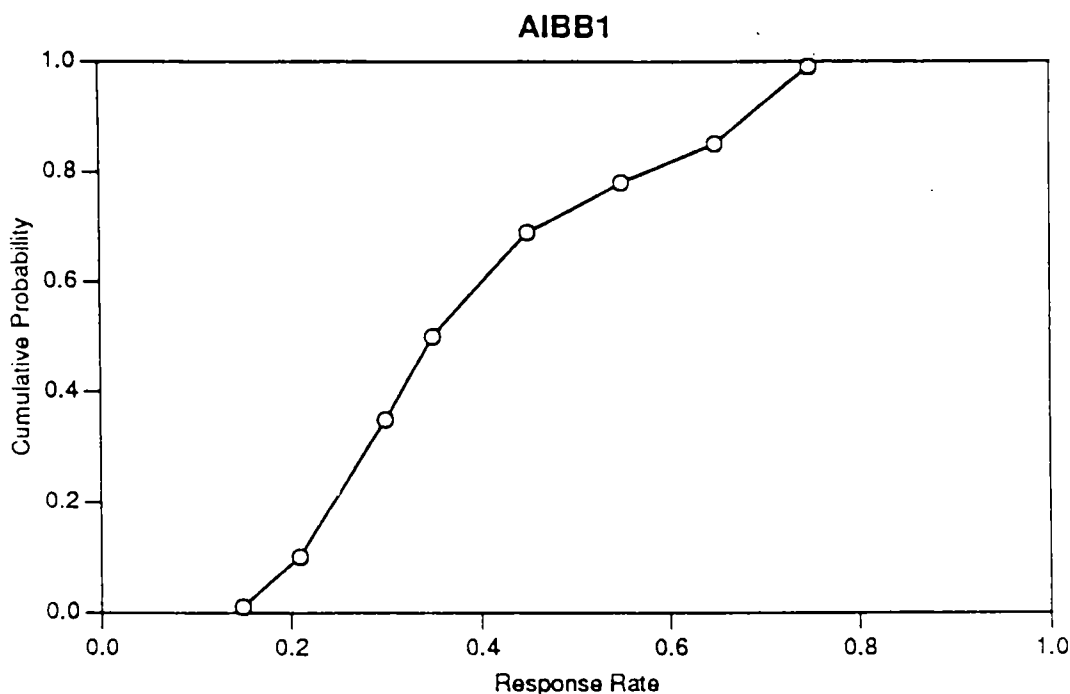


FIGURE 1 Cumulative Probability Distribution over Response Rate at a Personal Exposure Level of 0.025 ppm for Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season (AIBB1)

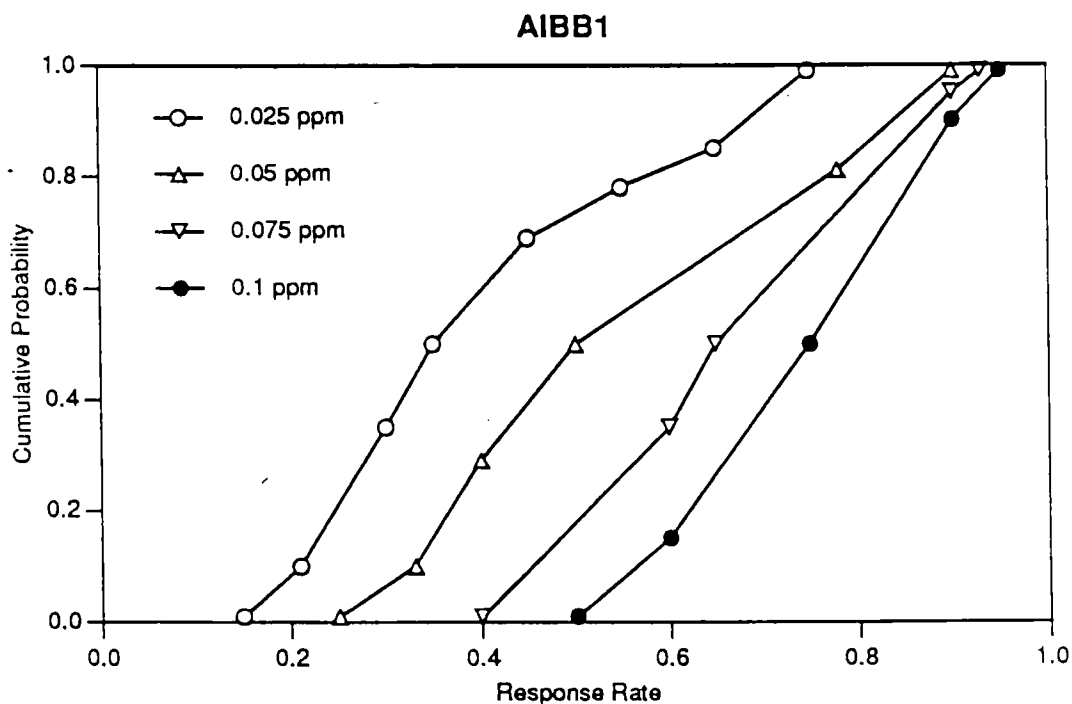


FIGURE 2 Cumulative Probability Distributions over Response Rates at Personal Exposure Levels of 0.025, 0.050, 0.075, and 0.100 ppm for Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season (AIBB1)

valid cumulative probability distribution. The nonintersecting property is important from a logical point of view; the intersection of two curves would imply that response rates above the intersection are more likely at the lower than at the higher concentration and that the converse is true for response rates below the intersection. Also note that the 0.050-ppm curve lies to the right of the 0.025-ppm curve, that the 0.075-curve lies to the right of the 0.050-ppm curve, and so on. This progression is logical because the response rate is expected to increase as the exposure level (i.e., ozone concentration) increases.

If an expert's assessments violated any of these conditions, we alerted him or her and tried to resolve the "inconsistency." Thus, in a sense, we "forced" the experts to provide "consistent" probability judgments. The judgments of all the experts are tabulated in Appendix C and summarized in Sections 3.1.2 and 3.1.3.

3.1.2 Exposure-Response Relationships

As shown in Figure 2, the median judged response rates at ozone concentrations of 0.025, 0.050, 0.075, and 0.100 ppm are 0.35, 0.50, 0.65, and 0.75, respectively, for Expert A. These ozone-concentration and response-rate pairs define the median exposure-response relationship shown in Figure 3. An additional point is shown at the origin of the graph because no ozone-induced lesions will, by definition, occur at an ozone concentration of 0 ppm.

Response rates corresponding to cumulative probabilities of 0.05 and 0.95 can be determined from Figure 2 by interpolation. For example, for the 0.025-ppm curve, a response rate of 0.18 corresponds to a cumulative probability of 0.05 (called the 0.05 fractile), and a response rate of 0.71 corresponds to the 0.95 fractile. Thus, the response rates of 0.18 and 0.71 define the central 90% CI at 0.025 ppm for Expert A. In a similar fashion, the 0.05 and 0.95 fractiles at the other ozone concentrations can be determined and the results drawn as a series of exposure-response relationships like those shown in Figure 4. These curves are monotonic increasing (because the response increases as the exposure increases) and converge at the origin.

Curves like those shown in Figure 4 depict the uncertainty in Expert A's judgments about the relationship between ozone exposure and the occurrence of ozone-induced lesions in the centriacinar region of the lungs of children living in Los Angeles. If Expert A were certain about this relationship, only one curve would be needed to completely characterize this belief. Since Expert A happens to be uncertain about this relationship, curves at any fractiles of interest could be shown; for simplicity, we present curves only for the 0.05, 0.5, and 0.95 fractiles.

Recall that we elicited the judgments of six experts about the relationship between ozone exposure and the occurrence of lesions in the centriacinar region of the lung. Judgments were elicited for conditions determined by all combinations of the occurrence of mild and moderate lesions, the locations of New York and Los Angeles, the populations of children and outdoor workers, and exposure for 1 and 10 ozone seasons. The possible combinations of lesion type, city, population of interest, and number of ozone seasons define 16 cases. To make it easier to refer to a particular case, the following four- or five-character code is used. The format for the code is lcps, where:

- l denotes lesion type (I for mlild or O for mOderate),
- c denotes city (L for Los Angeles, N for New York, or B for Both),

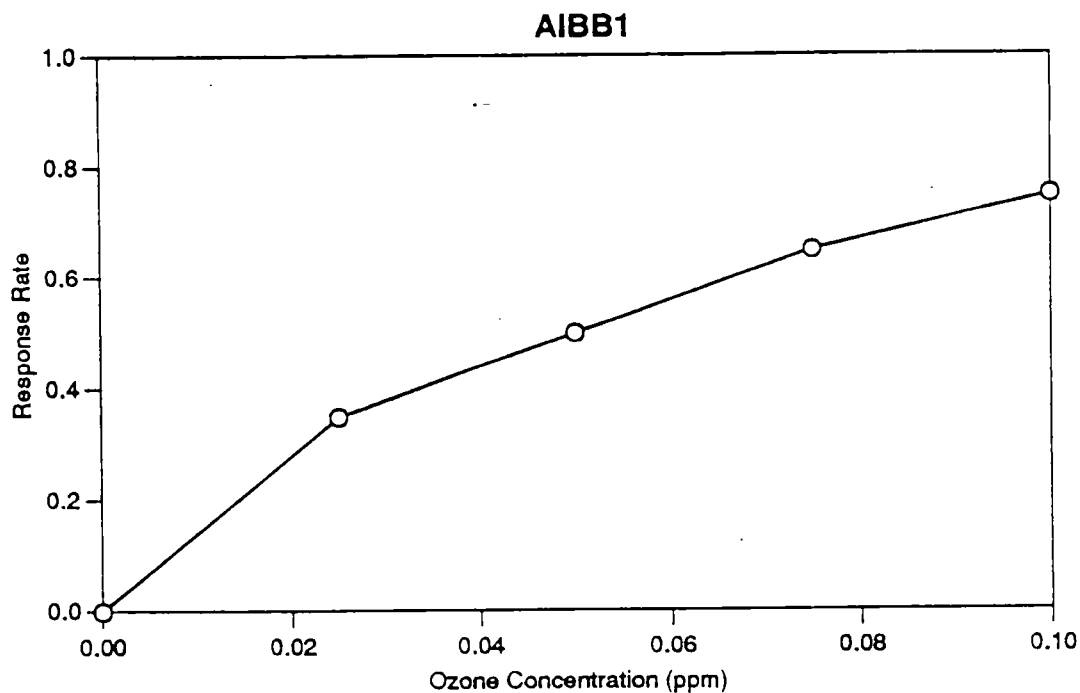


FIGURE 3 Median Exposure-Response Relationship for Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season (AIBB1)

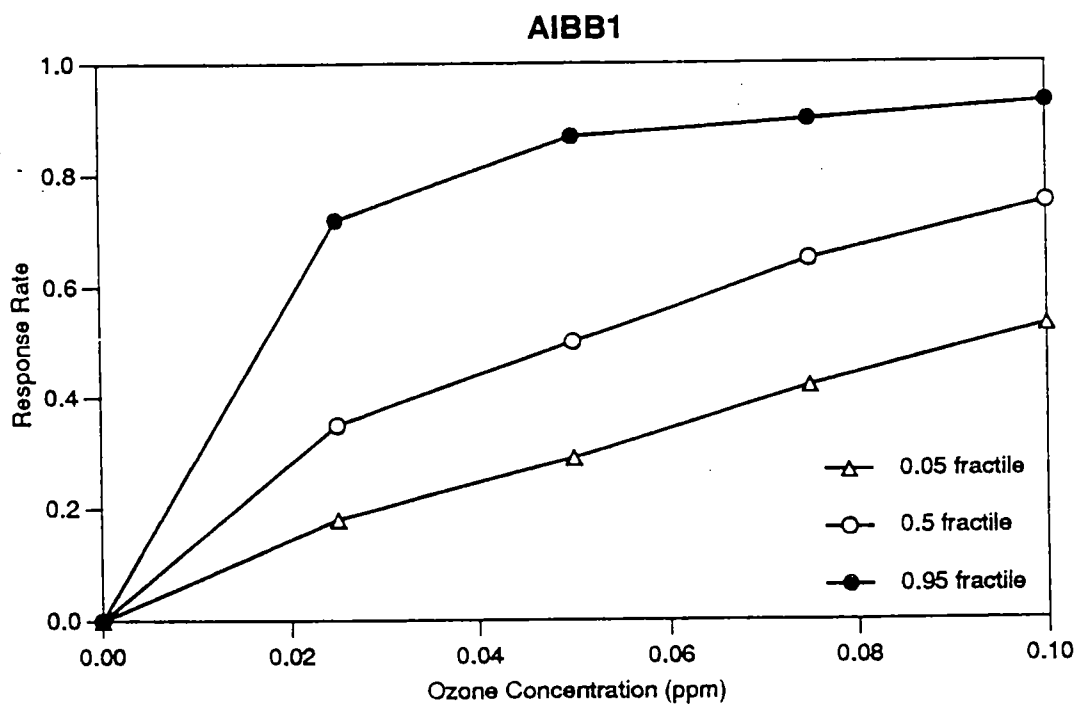


FIGURE 4 0.05-Fractile, Median, and 0.95-Fractile Exposure-Response Relationships for Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season (AIBB1)

p denotes population (C for Children, W for Workers, or B for Both), and

s denotes the number of ozone seasons (1, 10, or B for Both).

For example, ILC1 denotes the case for mild lesions, Los Angeles, children, and one ozone season.

For each case, judgments were sought about four ozone concentrations: 0.025, 0.050, 0.075, and 0.100 ppm. Thus, we faced the possibility of having to encode 64 probability distributions for each expert. However, the experts believed, to varying degrees, that the information was insufficient to distinguish all 64 cases. For example, Expert A did not distinguish between children and outdoor workers, or between Los Angeles and New York. This pattern held for the formation of mild and moderate lesions and for exposure to ozone for 1 and 10 seasons. Thus, only four sets of judgments were provided by Expert A, with each set of judgments applying to four cases (i.e., one for each combination of lesion type and number of ozone seasons). Because other experts shared similar beliefs to varying degrees, we ended up with a total of 36 sets of judgments for the group of 6 experts, instead of the largest possible number of 96 sets.

Table 1 lists the sets of judgments obtained. The codes corresponding to the 16 cases are listed in the second column, and the codes for the sets of judgments provided by the experts are listed in the remaining columns. The format for the code used to denote a set of judgments from an expert is similar to that used to denote a case; it is a five- or six-character code in which the first letter identifies the expert (A, B, C, D, E, or F). In the table, there are 36 unique codes, and each applies to one or more cases. For example, the set of judgments denoted AIBB1 (for Expert A, mild lesions, both Los Angeles and New York, both children and outdoor workers, and one ozone season) applies to cases 1, 3, 5, and 7. Note that there are only four instances in which a set of judgments applies to a single case, and all of these were provided by Expert D. One of these is DILC10 (case 2).

Before we present the results for each of the experts, readers should view the content of Figure 4 in the format shown in Figure 5. Here, the median and 90% CI are not indicated by "curves." Instead, for each exposure level, circles denote the median judgments, and vertical bars above and below each circle indicate the central 90% CI. Because Expert A does not distinguish between children and outdoor workers, or between Los Angeles and New York, Figure 5 summarizes all of Expert A's judgments about the incidence of mild lesions after one season of ozone exposure. The notation AIBB1 indicates these facts by containing the letter B (for both) in the positions for population and location.

The set of four median and 90% CI judgments by Expert A is presented in Figure 6. The upper-left panel, which is the case for mild lesions and 1 ozone season, reproduces Figure 5. Clockwise, the other panels are for mild lesions and 10 ozone seasons, moderate lesions and 10 ozone seasons, and moderate lesions and 1 ozone season.

*The code for a set of judgments that applies to only one case does not contain the letter B (for both).

TABLE 1 Codes for Sets of Judgments that Were Obtained for Each Case

Case		Expert					
Number	Code	A	B	C	D	E	F
1	ILC1	AIBB1	BIBC1	CIBB1	DILB1	EILBB	FIBB1
2	ILC10	AIBB10	BIBC10	CIBB10	DILC10	EILBB	FIBB10
3	ILW1	AIBB1	BIBW1	CIBB1	DILB1	EILBB	FIBB1
4	ILW10	AIBB10	BIBW10	CIBB10	DILW10	EILBB	FIBB10
5	INC1	AIBB1	BIBC1	CIBB1	DINB1	EINBB	FIBB1
6	INC10	AIBB10	BIBC10	CIBB10	DINB10	EINBB	FIBB10
7	INW1	AIBB1	BIBW1	CIBB1	DINB1	EINBB	FIBB1
8	INW10	AIBB10	BIBW10	CIBB10	DINB10	EINBB	FIBB10
9	OLC1	AOBB1	BOBC1	COBB1	DOLB1	EOLB1	FOBB1
10	OLC10	AOBB10	BOBC10	COBB10	DOLC10	EOLB10	FOBB10
11	OLW1	AOBB1	BOBW1	COBB1	DOLB1	EOLB1	FOBB1
12	OLW10	AOBB10	BOBW10	COBB10	DOLW10	EOLB10	FOBB10
13	ONC1	AOBB1	BOBC1	COBB1	DONB1	EONB1	FOBB1
14	ONC10	AOBB10	BOBC10	COBB10	DONB10	EONB10	FOBB10
15	ONW1	AOBB1	BOBW1	COBB1	DONB1	EONB1	FOBB1
16	ONW10	AOBB10	BOBW10	COBB10	DONB10	EONB10	FOBB10

The results for the other five experts are summarized in Figures 7-11 in the same format as Figure 6. Figures 8 and 11 indicate that Experts C and F, like Expert A, do not distinguish between children and outdoor workers, or between Los Angeles and New York. However, Figure 7 shows that Expert B does distinguish between children and outdoor workers. Similarly, Figure 9 shows that Expert D always distinguishes between Los Angeles and New York, and distinguishes between children and outdoor workers only for Los Angeles and 10 ozone seasons. Finally, Figure 10 shows that Expert E always distinguishes between Los Angeles and New York and does not distinguish between 1 and 10 ozone seasons for mild lesions.

For all the experts, the judged median response rates are lower for moderate than for mild lesions. Nevertheless, for the moderate lesions, with the exception of Expert E, the median response rates are greater than 0 at 0.075 and 0.100 ppm for 1 ozone season and at 0.050, 0.075, and 0.100 ppm for 10 ozone seasons. For Expert E, the median response rate exceeds 0 only at 0.100 ppm for 1 season and at 0.075 and 0.100 ppm for 10 seasons.

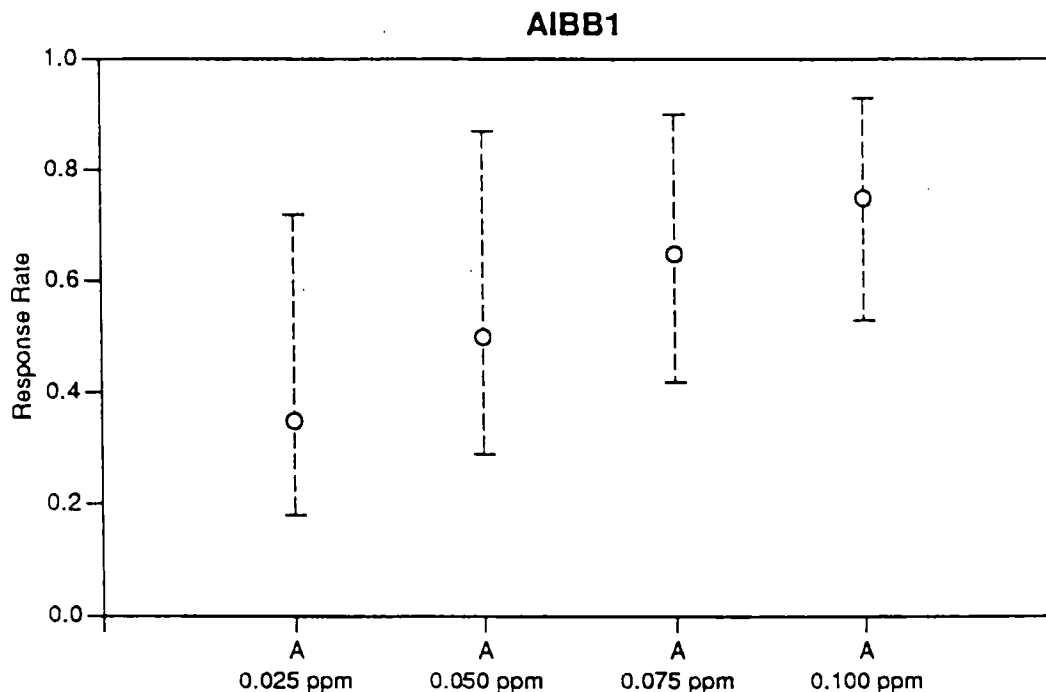


FIGURE 5 Median and 90% CI Judgments of Expert A for Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, and One Ozone Season (AIBB1)

3.1.3 Comparisons across Experts

While Figures 6-11 indicate the judgments of each expert clearly, they do not facilitate comparisons across experts. For that purpose, we provide Figures 12-15.

Figure 12 represents the 4 combinations of mild versus moderate lesions and 1 versus 10 ozone seasons for children in Los Angeles (cases 1, 2, 9, and 10 in Table 1). The two top panels are for mild lesions, and the two bottom panels are for moderate lesions; the two left-hand panels are for 1 ozone season, and the two right-hand panels are for 10 ozone seasons. This figure provides insight into the similarities and differences across experts in their judgments of central tendency (median responses) and in the uncertainty in their judgments (90% CIs). The results for the experts are grouped according to mean ozone level along the horizontal axis. A symbol (circle, square, or diamond; filled or not filled) denotes the median (0.5 fractile) response elicited from an expert. Vertical bars (of different styles to help distinguish between the experts) above and below the median symbol denote the 0.95- and 0.05-fractile responses elicited. These vertical bars denote the 90% CI about the median. For example, recall from the previous discussion of Expert A's judgments that for case 1 at 0.025 ppm the median response rate is 0.35 and that the 90% CI is 0.18 to 0.71. Those values are indicated in Figure 12 in the area for 0.025 ppm and Expert A. In the figure, the case (ILC1) is indicated above the graph. The legend indicates the set of judgments that applies to the case for each expert. These are AIBB1 for Expert A, BIBC1 for Expert B, and so forth.

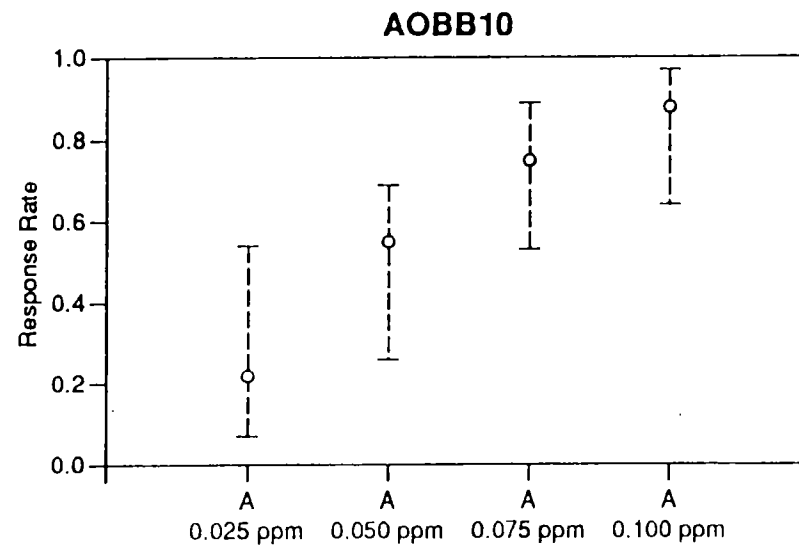
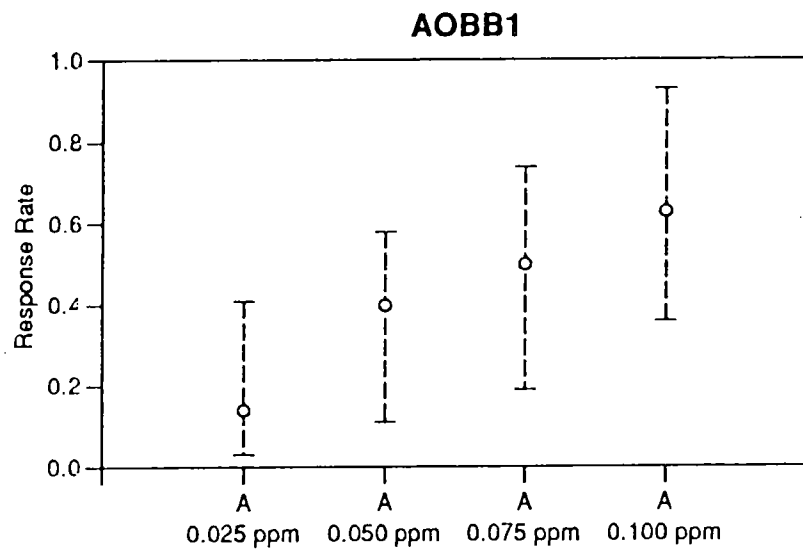
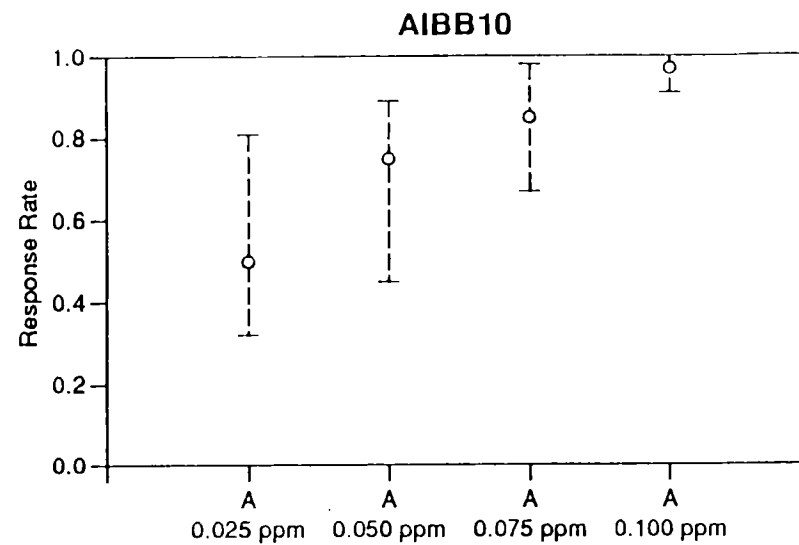
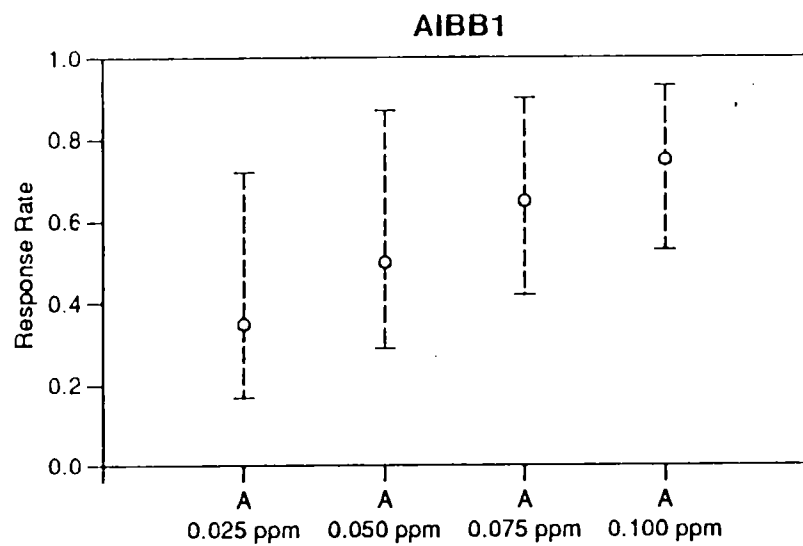


FIGURE 6 Median and 90% CI Judgments of Expert A

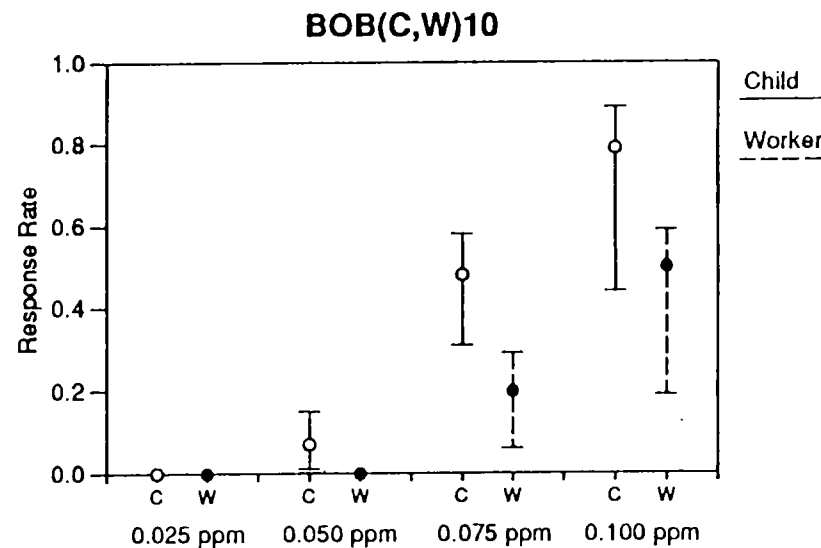
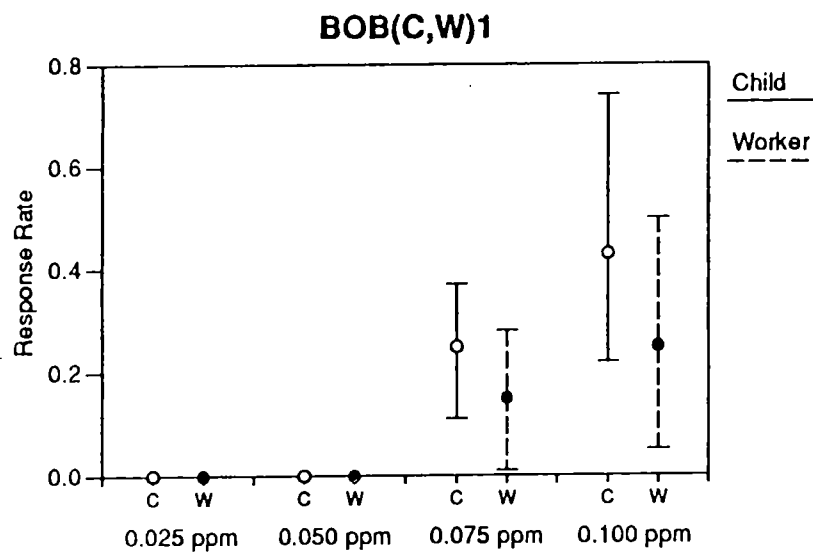
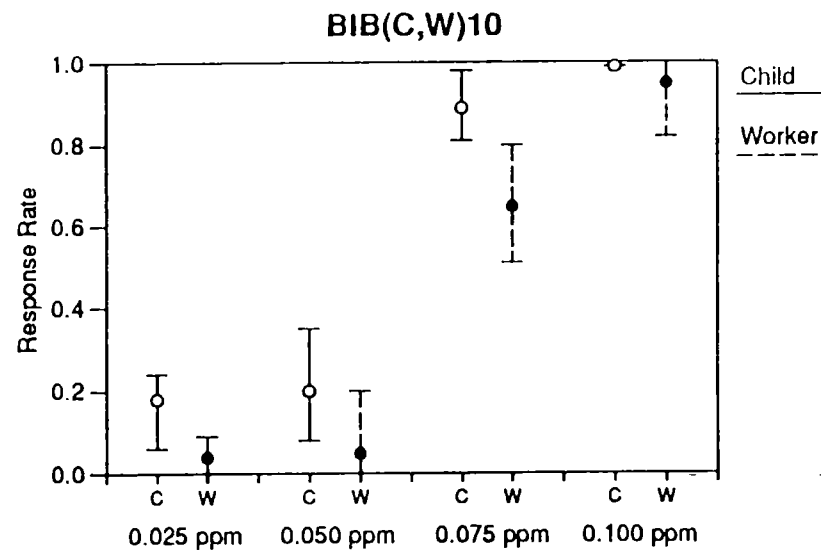
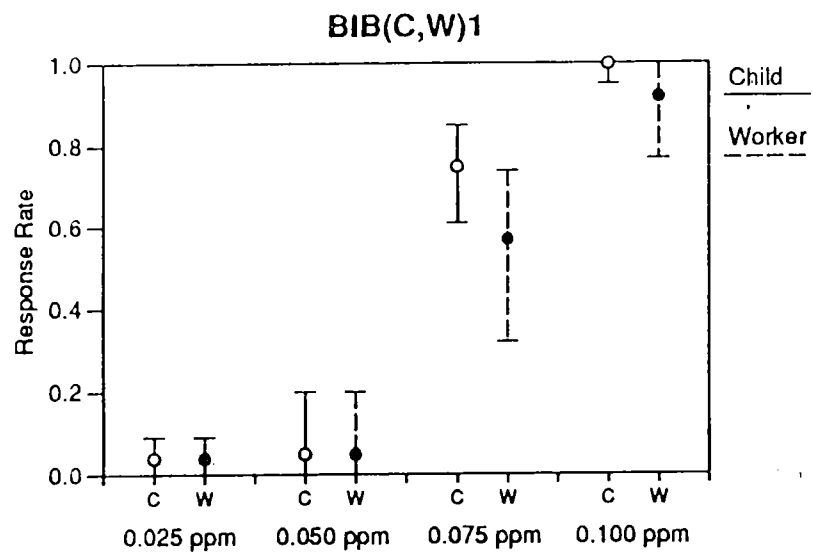


FIGURE 7 Median and 90% CI Judgments of Expert B

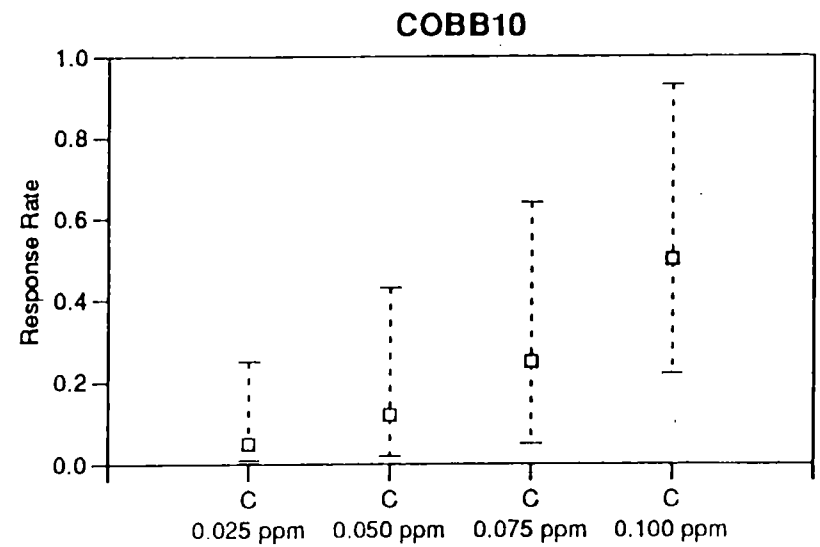
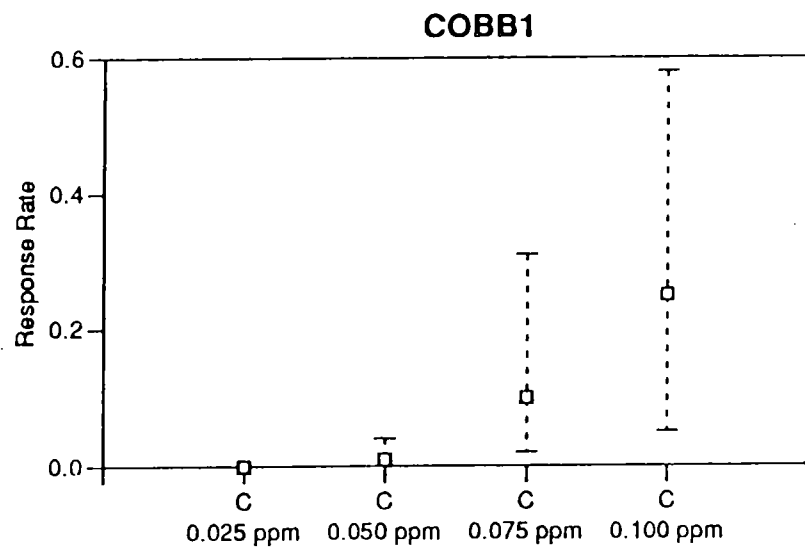
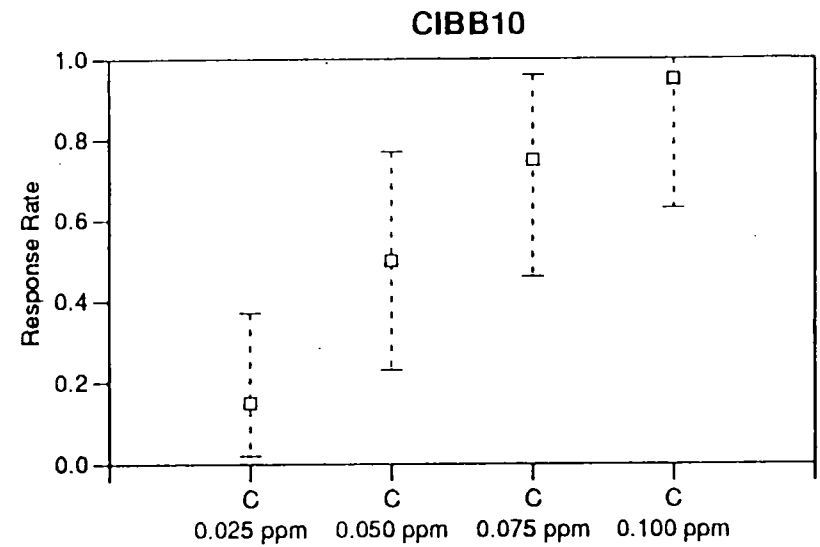
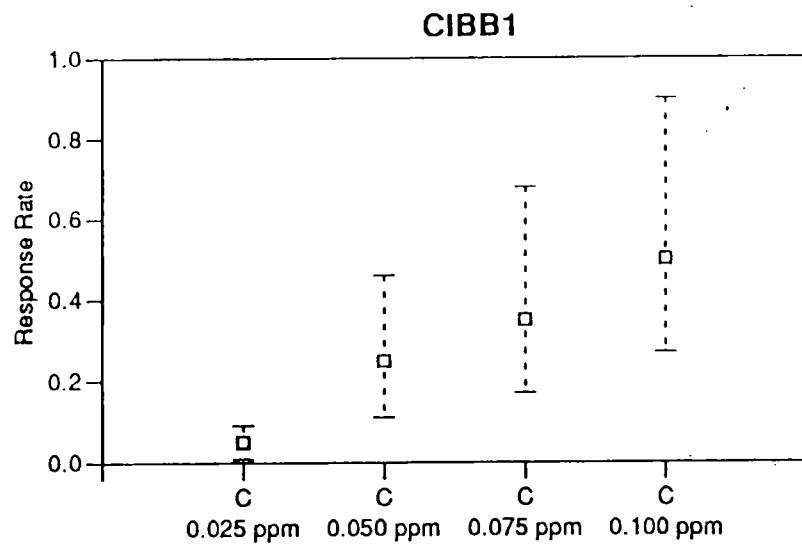


FIGURE 8 Median and 90% CI Judgments of Expert C

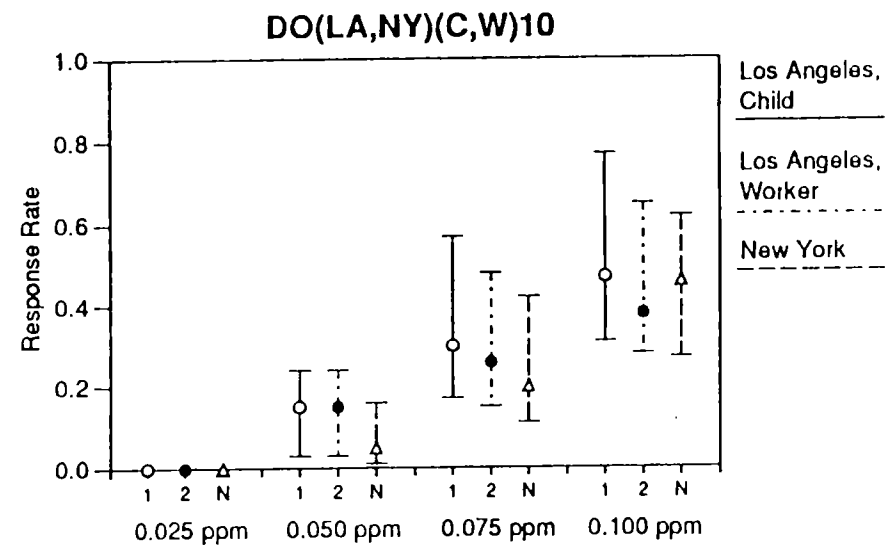
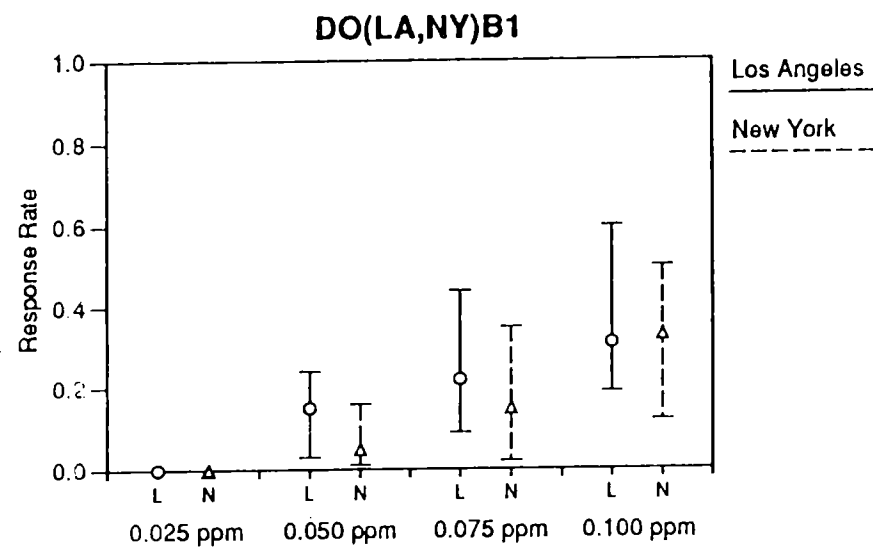
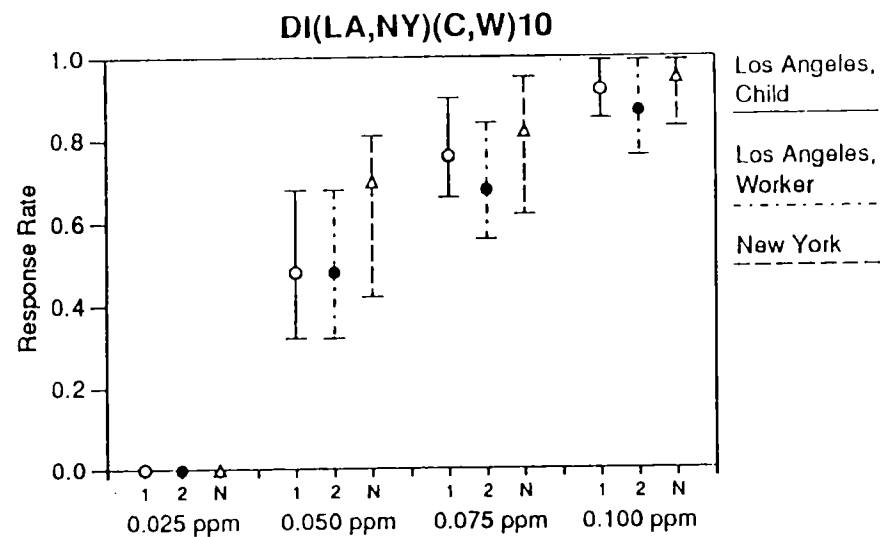
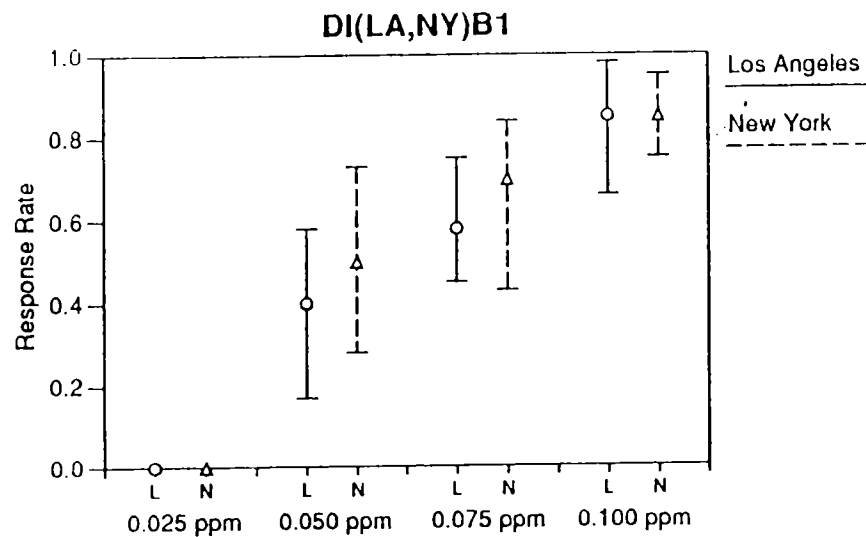


FIGURE 9 Median and 90% CI Judgments of Expert D

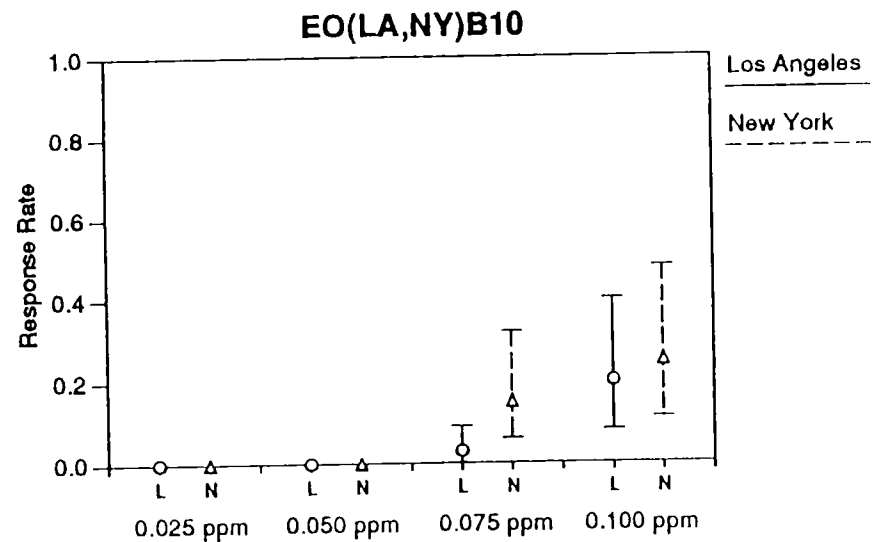
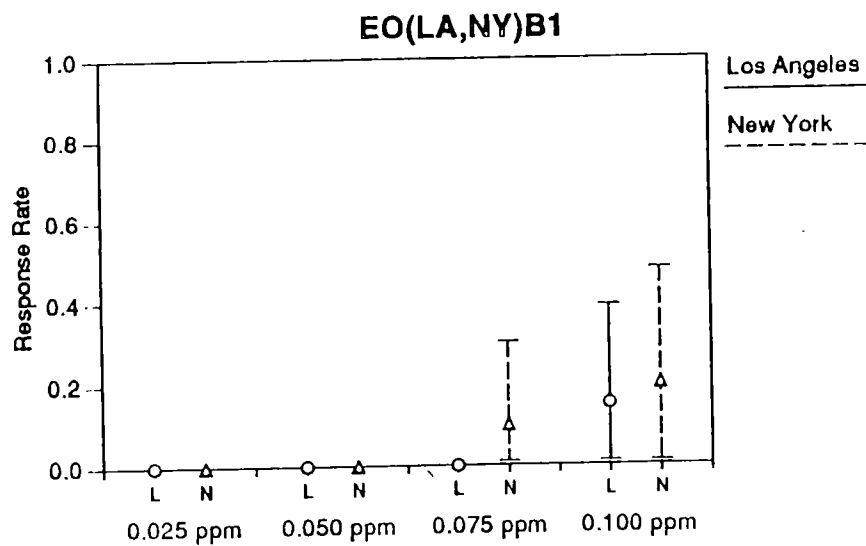
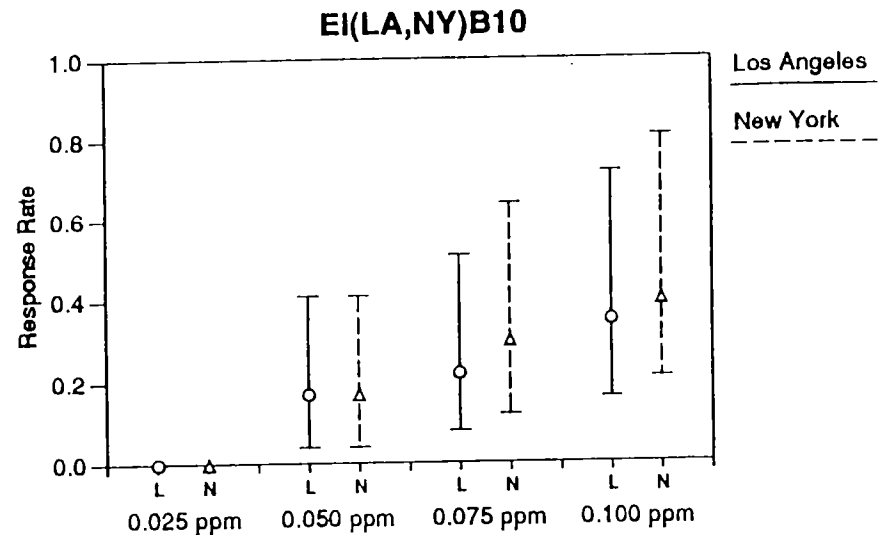
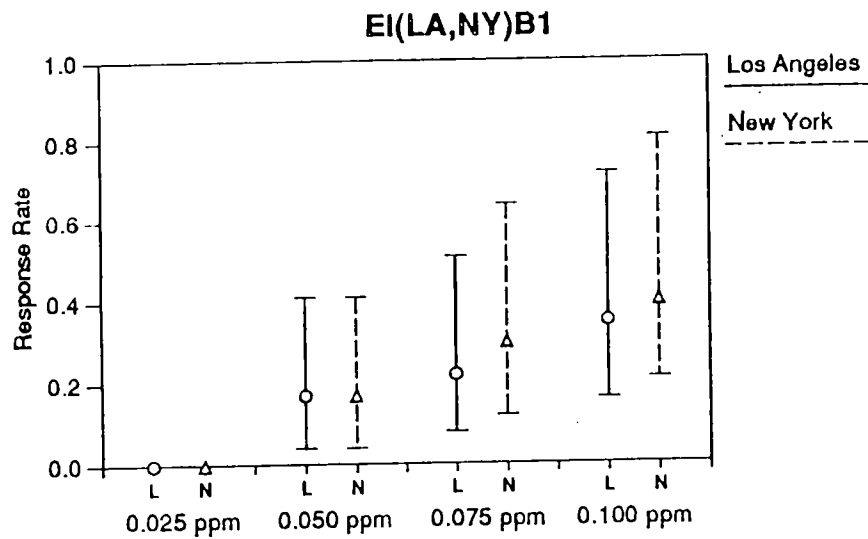


FIGURE 10 Median and 90% CI Judgments of Expert E

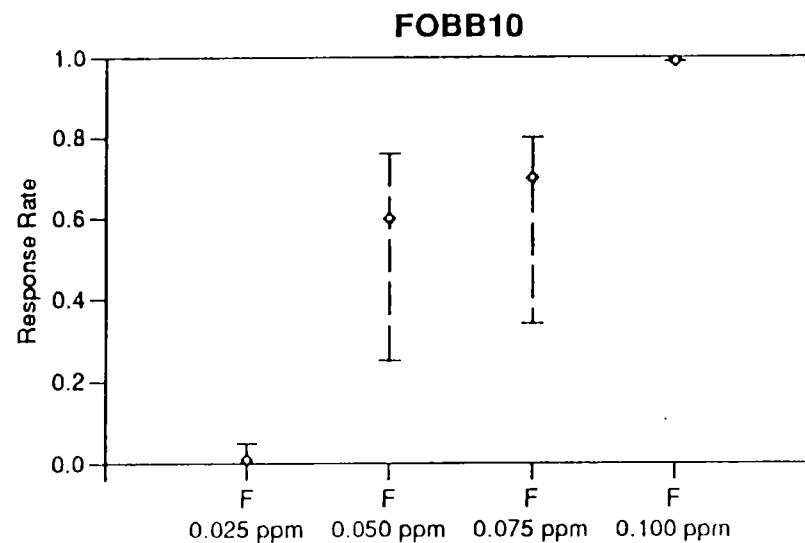
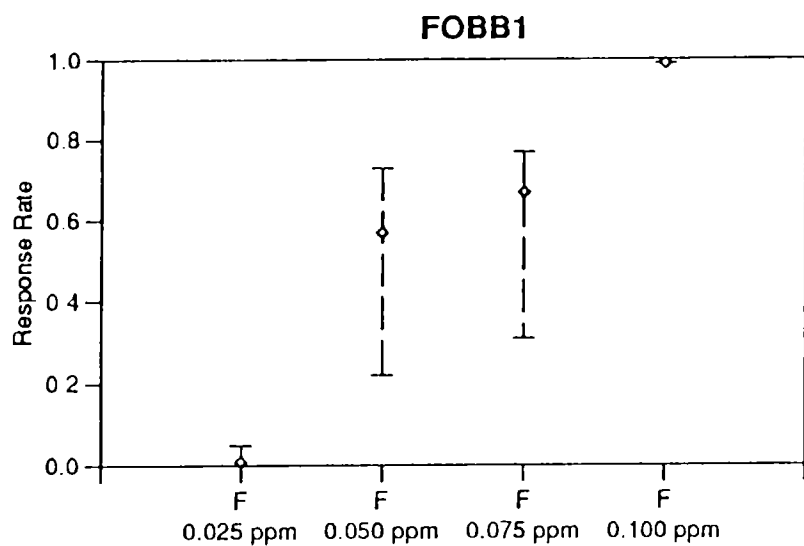
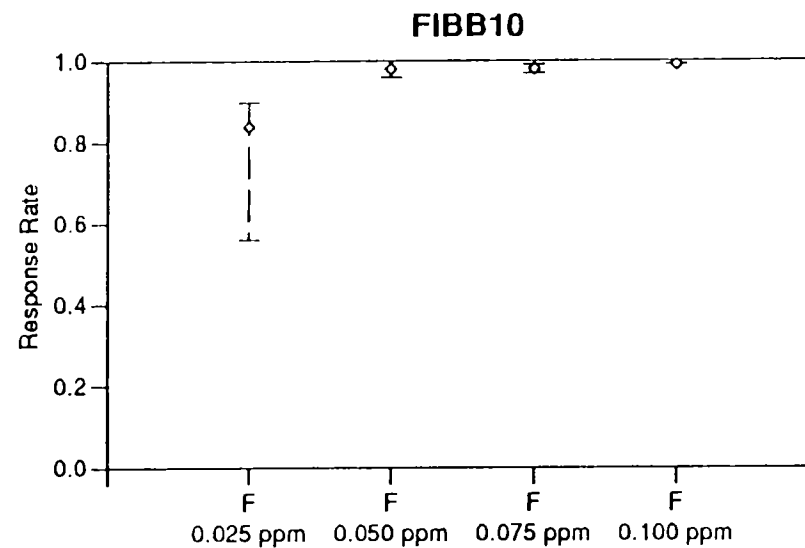
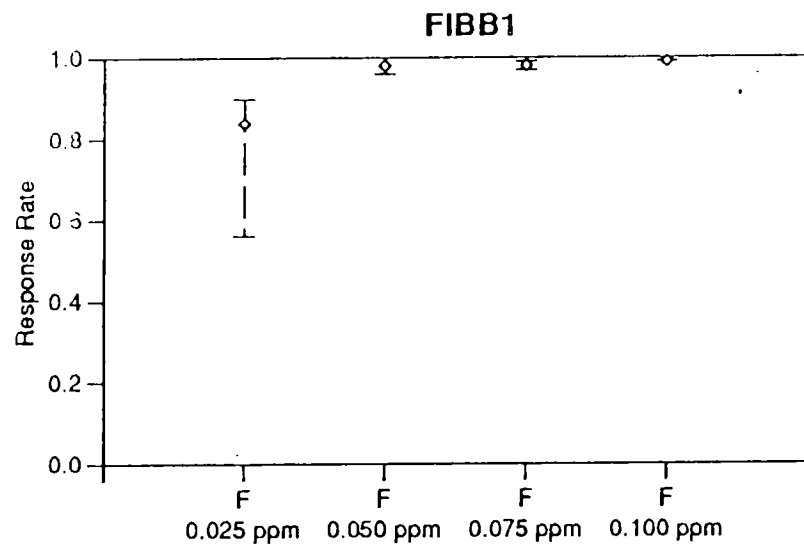


FIGURE 11 Median and 90% CI Judgments of Expert F

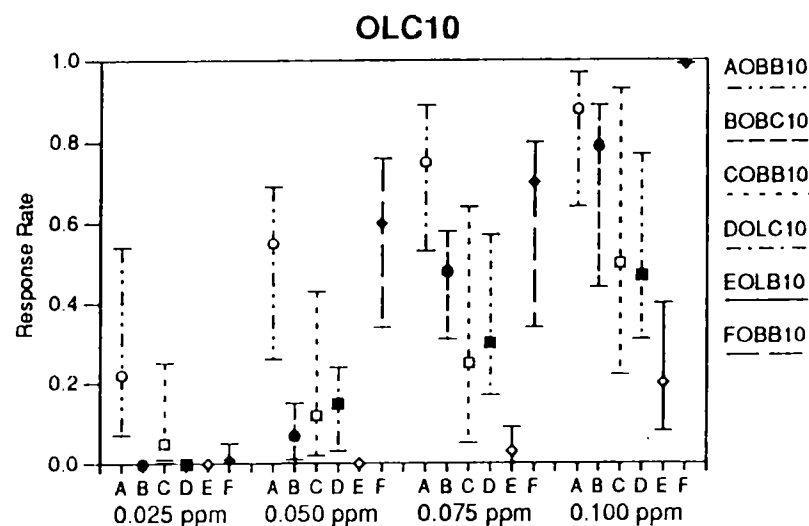
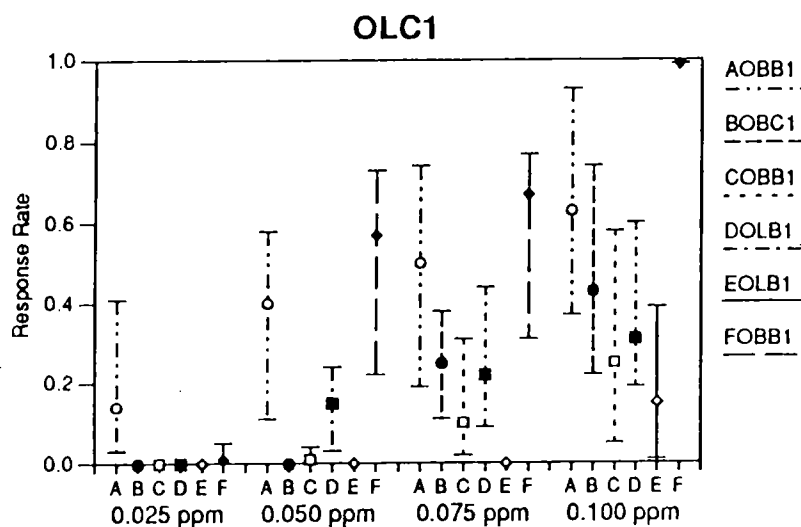
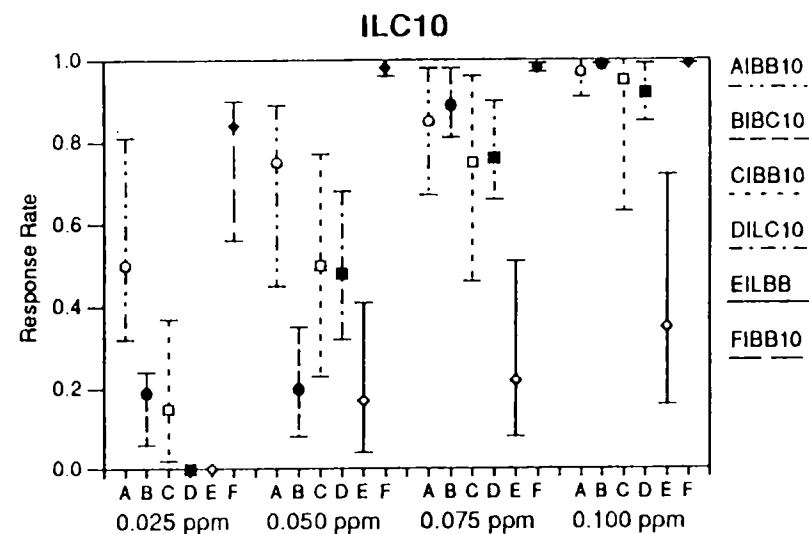
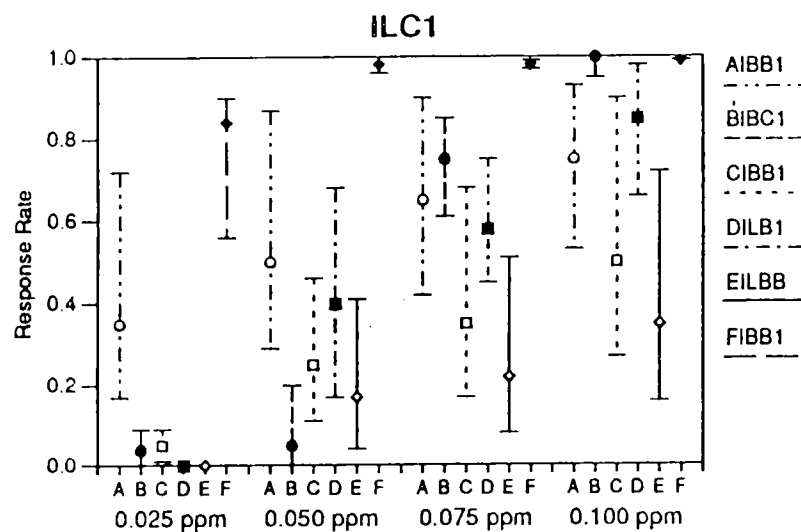


FIGURE 12 Medians and 90% CIs for Judgments about Mild and Moderate Lesions, Children, Los Angeles, and 1 and 10 Ozone Seasons (summarized are all the judgments for Experts A, C, and F, that is, the experts who did not distinguish populations or locations; differences in judgments for Experts B, D, and E as a function of these factors are shown in Figures 13-15)

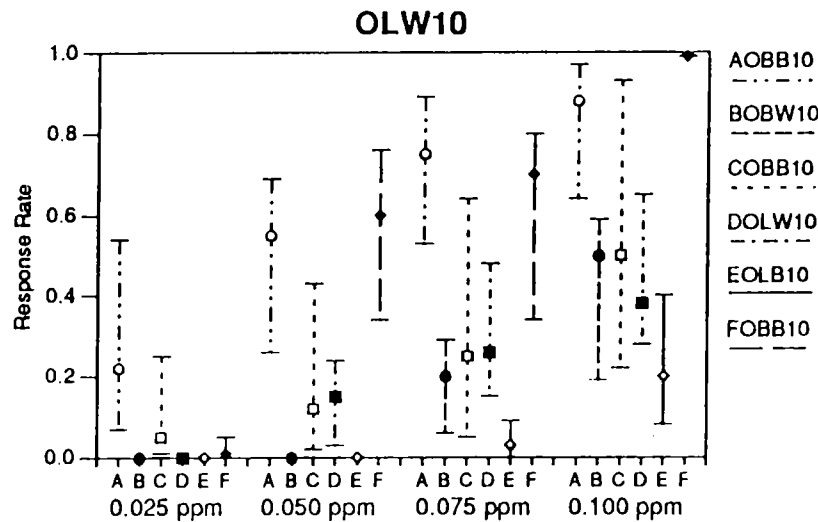
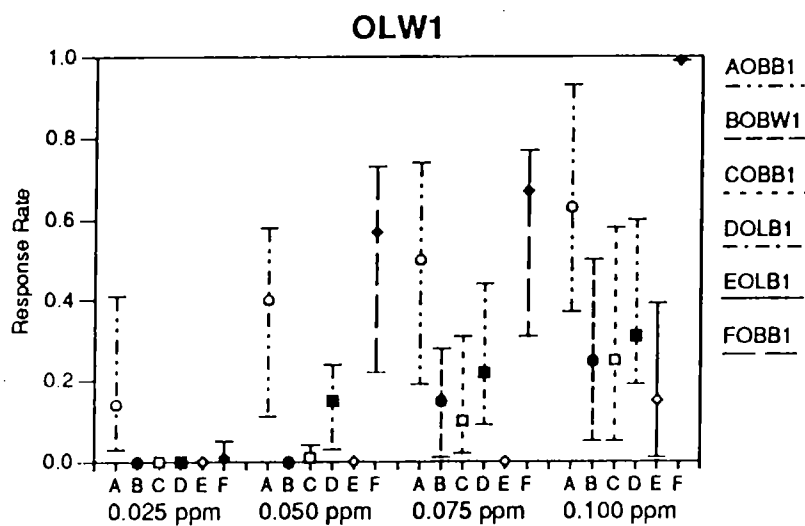
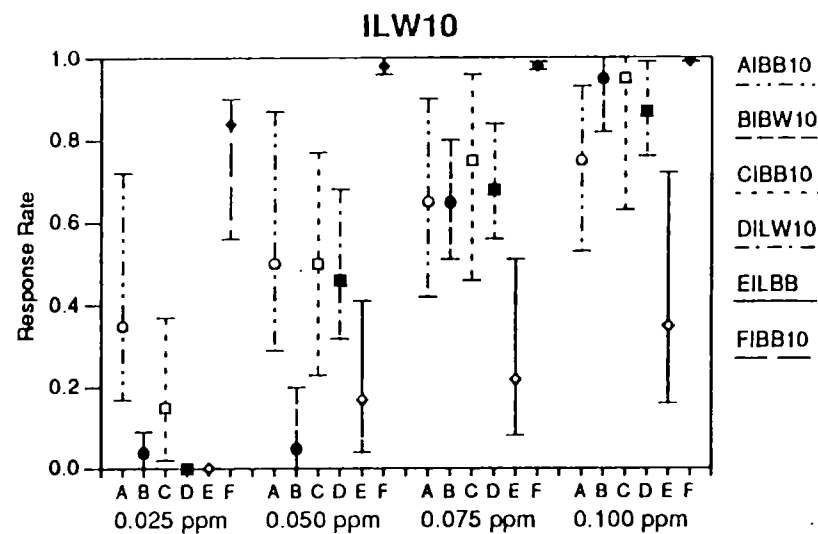
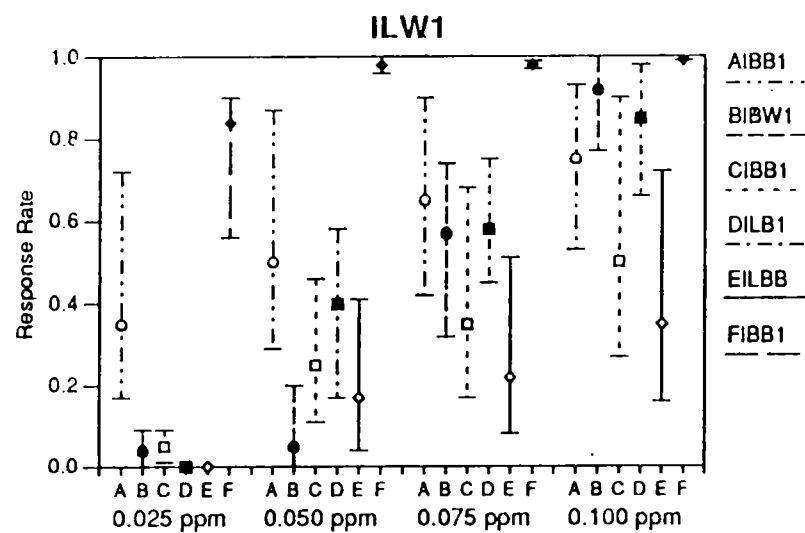


FIGURE 13 Medians and 90% CIs for Judgments about Mild and Moderate Lesions, Outdoor Workers, Los Angeles, and 1 and 10 Ozone Seasons

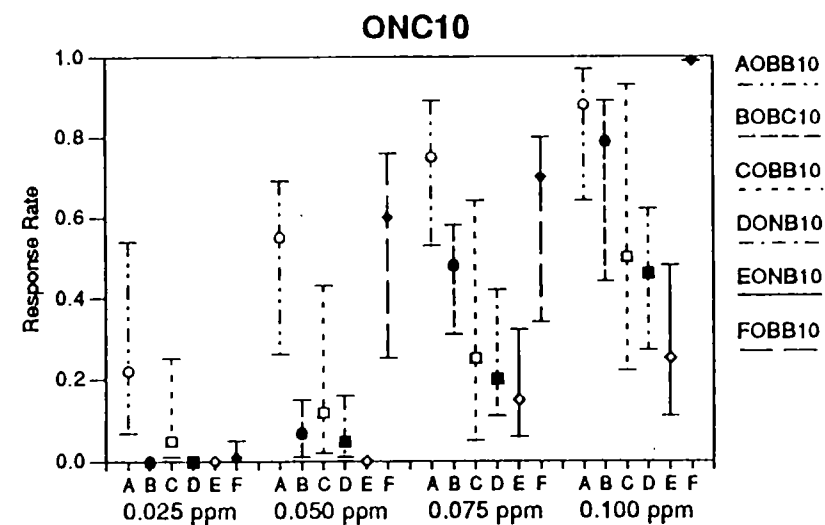
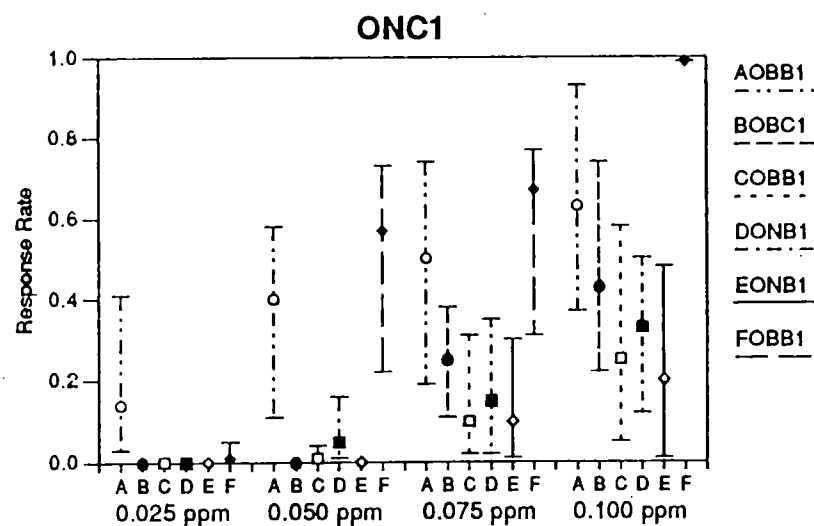
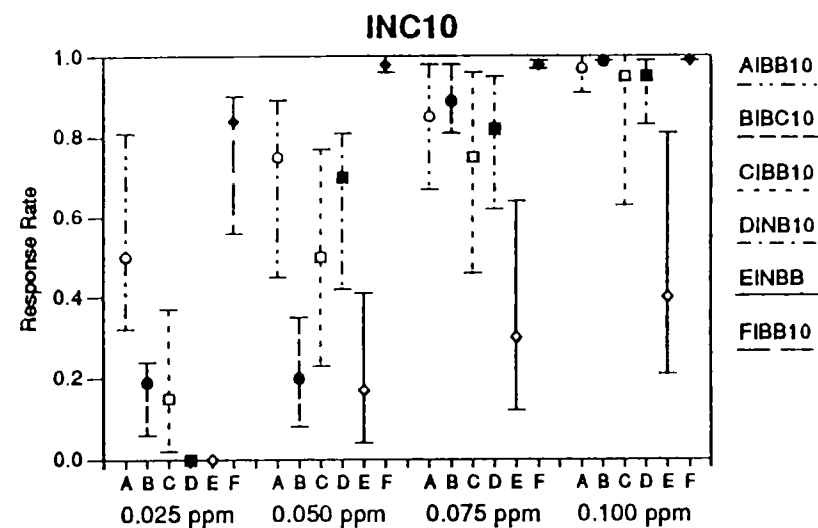
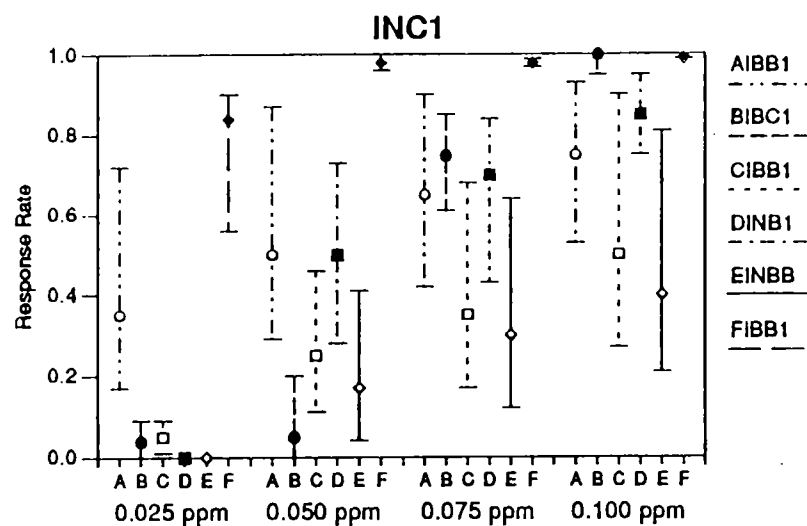


FIGURE 14 Medians and 90% CIs for Judgments about Mild and Moderate Lesions, Children, New York, and 1 and 10 Ozone Seasons

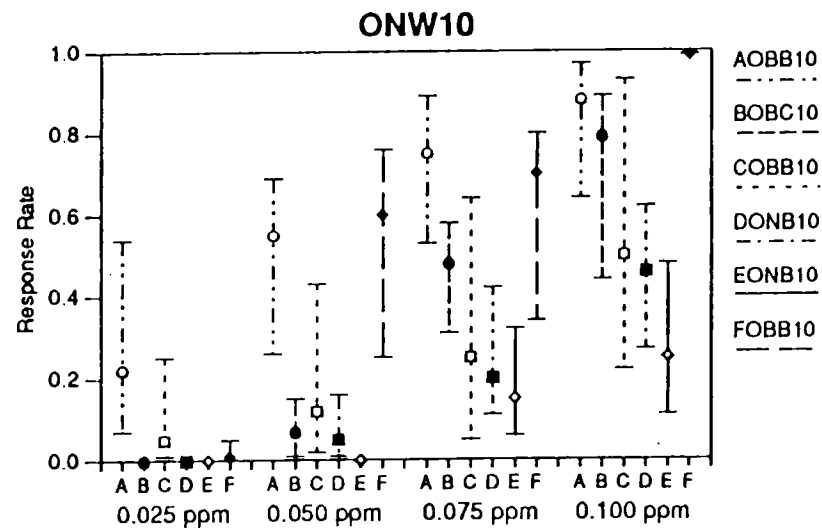
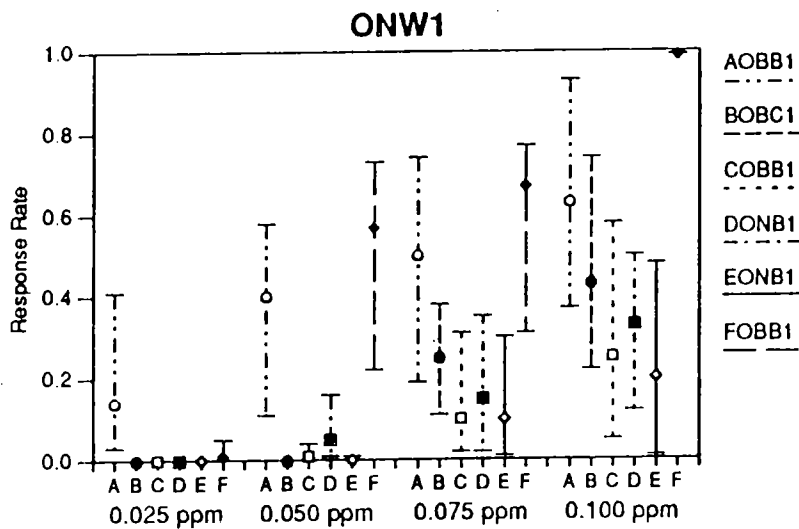
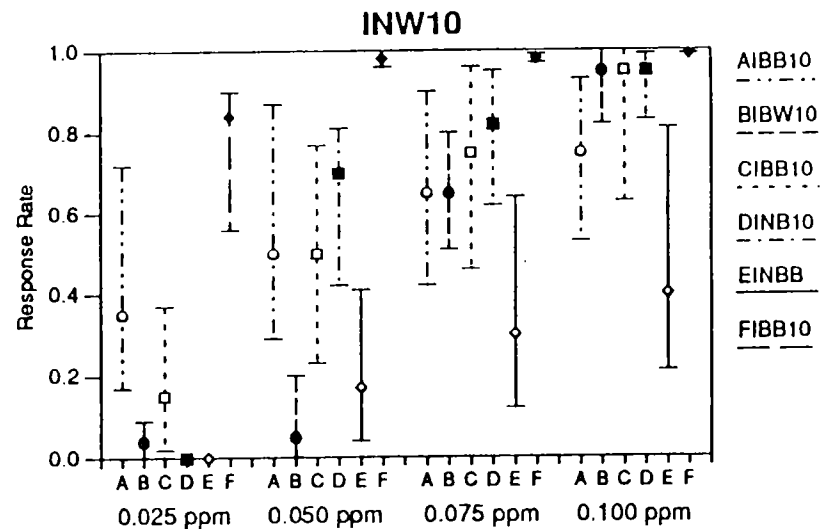
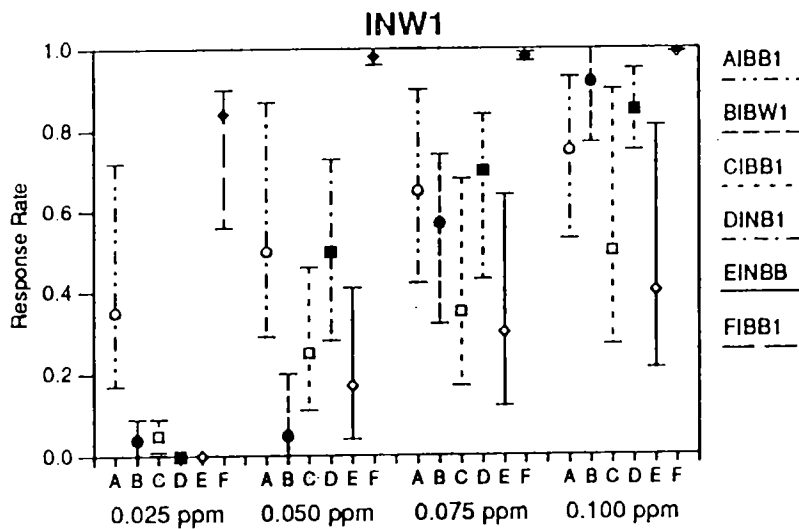


FIGURE 15 Medians and 90% CIs for Judgments about Mild and Moderate Lesions, Outdoor Workers, New York, and 1 and 10 Ozone Seasons

Figures 13-15 are similar to Figure 12. Whereas Figure 12 summarizes the results for all of the experts for children in Los Angeles, Figures 13-15, respectively, do the same for outdoor workers in Los Angeles, children in New York, and outdoor workers in New York. Figures 12-15 contain a great deal of information, and the objective of the rest of this section is to interpret some of these quantitative results. The intent is to highlight important similarities, differences, and trends rather than to dwell on specific numbers. When numbers are used in the comparisons, they are usually taken directly from Figures 12-15. On occasion, the numbers represent averages. For example, the number may be an average of median response rates across Los Angeles and New York for experts who stratify by location when the comparison of interest does not involve location.

The discussion is organized into the following nine topics: mild versus moderate lesions, children versus outdoor workers, Los Angeles versus New York, 1 ozone season versus 10 ozone seasons, effects of ozone concentrations, medians, degree of uncertainty, degree of overlap in the 90% CIs, and existence of ozone-induced lesions.

Mild versus Moderate Lesions. As might be expected, with all else equal, the experts judged that a higher percentage of the populations of interest would form mild lesions rather than moderate lesions. However, the mild as against moderate distinction varied across experts. For Expert A, the response rate was slightly higher for mild lesions, with medians typically indicating that an additional 10-15% of the populations of interest would develop mild lesions as compared with those developing moderate lesions. Experts C, E, and F judged the response rates for mild lesions to be quite a bit higher than those for moderate lesions. For Expert B, mild lesions were substantially more likely than moderate lesions at levels above 0.050 ppm; for Expert D, mild lesions were substantially more likely than moderate lesions at levels above 0.025 ppm. Several medians were about 0.50 higher for mild lesions as against moderate lesions, indicating that an extra 50% of the populations of interest would be expected to develop lesions if the definition of a lesion were expanded to include mild as well as moderate ones.

Children versus Outdoor Workers. Expert B (for all cases) and Expert D (for Los Angeles) distinguished between children and outdoor workers, giving slightly higher response rates for children.

Los Angeles versus New York. Only Experts D and E distinguished between locations. Expert D gave New York response rates that were slightly higher than those for Los Angeles for mild lesions but reversed this conclusion for moderate lesions. Expert E gave New York response rates that were slightly higher than those for Los Angeles for both mild and moderate lesions.

One Ozone Season versus Ten Ozone Seasons. As might be expected, higher response rates were given for 10 ozone seasons than for 1 ozone season. However, Expert E did not differentiate between results for 1 season and 10 seasons for mild lesions, and Expert F had only very minor differences between 1 and 10 seasons. Expert D had small differences (median shifts of 0-0.16); Experts A and B had moderate differences (median shifts of 0.08-0.25 for the former and 0-0.31 for the latter); and Expert C had substantial differences (median shifts of 0.05-0.45).

Effects of Ozone Concentrations. As the ozone concentration increased, the proportion of the population expected to develop lesions also increased. The nature of the increases varied somewhat across the experts. Expert B's fractiles showed a very big jump from the 0.050-ppm level to the 0.075-ppm level. For example, Expert B's 90% CIs implied that 8-35% of children would develop mild lesions over 10 ozone seasons at 0.050 ppm, but 81-98% would develop such lesions at 0.075 ppm. Expert D had a big jump for the case of mild lesions in going from 0.025 ppm to 0.050 ppm. Expert F had a big jump for the case of moderate lesions in going from 0.025 ppm to 0.050 ppm. For the other experts (and in the other cases for Experts D and F), the changes in response rates were more even in moving from 0.025 ppm through 0.050 ppm and from 0.075 ppm to 0.100 ppm. For example, Expert A's medians for the one-season case were 0.35, 0.50, 0.65, and 0.75 for the four exposure levels.

Medians. The median response rates varied from expert to expert, but there was some consistency in terms of relative levels. Overall, Expert F had the highest medians; all were above 0.50, except for the case of moderate lesions at 0.025 ppm. Expert A also had somewhat higher medians. Expert B was on the low side for 0.025 ppm and 0.050 ppm, but somewhat on the high side for higher ozone concentrations. Expert D fell more or less in the middle. The medians for Expert C were slightly low relative to the other experts. Expert E had the lowest medians overall; they went only as high as 0.38 for mild lesions and 0.22 for moderate lesions.

Degree of Uncertainty. One measure of the degree of uncertainty felt by the experts was the width of their 90% CIs, with a wider interval indicating greater uncertainty about the response rate. Expert F had relatively narrow intervals, except for moderate lesions at ozone concentrations of 0.050 ppm and 0.075 ppm. For the most part, Expert B's intervals were not very wide, with several narrower than 0.10 and only a few with widths above 0.40. Expert D showed no uncertainty at 0.025 ppm and a moderate amount of uncertainty at higher levels. Similarly, Expert E displayed no uncertainty at low levels and a fair amount of uncertainty at higher levels. Expert A's intervals were generally quite wide, with all but one wider than 0.25 and several wider than 0.50. Most of Expert C's intervals were very wide, with many wider than 0.50 and one as wide as 0.71. The maximum possible width of 1.00 would include all response rates from zero to one.

Degree of Overlap in the 90% CIs. As indicated above, the experts differed in terms of their medians and the widths of their 90% CIs. The degree to which the 90% CIs of different experts overlapped varied from case to case. Experts B, C, and D overlapped in almost all cases. There was a tendency for Expert F's intervals to be higher than the others (overlapped the least) and for Expert E's intervals to be lower (overlapped sometimes). Expert A's intervals were sometimes higher than most of the others, but they overlapped with those of Experts B, C, and D for the higher ozone concentrations.

Existence of Ozone-Induced Lesions. The most important question was whether, in the judgments of the experts, ozone-induced lesions would form in the populations of interest under the stated conditions. The situations that could logically be viewed as most likely to lead to such formation are those involving mild lesions after 10 seasons of exposure. At the lowest exposure level (0.025 ppm), Experts D and E judged that there would be no response; Experts B and C expected a low response (medians of 0.12 and 0.15, and 0.05 fractiles of 0.03 and 0.02);

and Experts A and F predicted much higher response rates (medians of 0.50 and 0.85, and 0.05 fractiles of 0.32 and 0.56). At the next highest exposure level (0.050 ppm), Experts B and E had medians of 0.12 and 0.17, whereas the other experts had medians of 0.50 and above; all 0.05 fractiles were above zero, implying that all experts judged that, with a probability of at least 0.95, there would be *some* response. At 0.075 ppm, only Expert E had a median below 0.75 and a 0.05 fractile lower than 0.45. At 0.100 ppm, even Expert E had a 90% CI from 0.18 to 0.76. All the others expected higher response rates.

At the other end of the spectrum are the situations expected to be least likely to lead to a response, that is, those involving moderate lesions after exposure for one season. At 0.025 ppm, four experts judged that there would be no response; Expert F had a 90% CI of 0 to 0.05, and Expert A had a 90% CI of 0.03 to 0.41. At 0.050 ppm, Experts B, C, and E were still confident that the response rate would be zero or very close to zero; 90% CIs for the other experts were 0.02-0.20 (Expert D), 0.10-0.58 (Expert A), and 0.21-0.73 (Expert F). At 0.075 ppm, the medians ranged from 0.05 to 0.67. Finally, at 0.100 ppm, Expert F was virtually certain of a 100% response. The other medians ranged from 0.17 to 0.63; the 0.05 fractiles ranged from 0.01 to 0.37. These results indicate that, in the judgments of the experts, formation of ozone-induced lesions in the centriacinar region under the stated conditions would be likely in at least some of the members of the populations of interest and, in some cases, in a substantial proportion of them.

3.2 QUALITATIVE JUDGMENTS

The qualitative judgments were obtained through discussions before and during the probability encodings in the first round and throughout the workshop. Although the discussions were structured by the encoding protocol in the first instance and by the workshop agenda and chairperson in the second, they tended to flow in various directions, depending on the participants and the particular points that arose. Also, by their very nature, qualitative judgments sometimes encompass a number of topics and are therefore difficult to categorize. Consequently, we found it harder to summarize comments and make comparisons across experts in the qualitative as against the quantitative case. Complete summaries of the discussions are found in Appendix D, organized topically within the first round of encodings (Section D.1) and by order of discussion within the workshop (Section D.2). As with the quantitative results, experts are identified by code letters. The highlights of these discussions are presented here for six major topics.

3.2.1 Definition of the Health Endpoint

The experts generally agreed that the focus on centriacinar lesions was appropriate. Experts A, B, E, and F stated this explicitly, and Expert C noted that the centriacinar region of the lung receives the highest dose of ozone in all species.

The reaction to the use of mild and moderate lesions, along with their definitions, was also basically favorable. Expert A called the definitions as good as one can come up with; Expert B commented that one does not normally think of lesions as mild or moderate but that the distinction is satisfactory for the purposes of this study; and Expert E believed that the definitions were clear but noted that they were limited to morphological lesions.

The experts sometimes thought about the mild/moderate distinction in different ways. Expert B thought in terms of a mild lesion being one that cannot be distinguished with routine histopathology techniques (e.g., paraffin) and a moderate lesion being one that can be so distinguished. Expert F interpreted mild as subtle and moderate as overt. Expert E questioned whether mild ozone-induced lesions could be detected in humans in light of their exposure to other environmental pollutants. The endpoint required the experts to think specifically about *ozone-induced* lesions. Expert F commented that an inventory of structures, or of centriacinar lesions, is needed.

3.2.2 Extrapolation from Animals to Humans

With respect to formation of centriacinar lesions, Expert A noted that no animal studied has failed to show at least some degree of lesion formation. The effects may be different in time and intensity, but the lesions are always present. As a result, Expert A believed that humans almost certainly get centriacinar lesions. Expert E commented that the results across species are likely to be "about the same" at cellular and subcellular levels. Animals are giving us the right leads, telling us what endpoints to look for and the exposure levels of concern. On the other hand, Expert D cautioned that, with some probability, the chronic effect will be lesions but that, for the remaining probability, the chronic effect will be emphysema. The animal data suggest that the probability of developing emphysema approaches zero, whereas the human data suggest that it is distinctly greater than zero.

As to the question of which studies are most useful, Expert B viewed primate studies as more useful than rat studies for extrapolating to humans because of similarities in structures and cell populations. Expert C cited "the low-dose work" as most useful, mentioning that some of the work on monkeys is "OK." Expert F believed that the most useful studies have been those involving chronic exposures and multiple endpoints and that studies with acute exposures have not been as helpful.

With respect to the dosimetry results, the experts expressed concern about some of the results and the values chosen for model parameters. For example, Expert B disagreed with the generation/airway definitions; Expert C argued that the assumption regarding recovery rate was too low and disagreed with the contention that nose breathing equals mouth breathing; and Expert A noted that the basic data needed to adjust the parameters are still missing, particularly as related to ventilation. The concerns were perhaps best summarized by Expert E: "I am wary of the model results." However, the general idea of dosimetry modeling was viewed very favorably. Expert A commented that dosimetry modeling is a good idea, noting that the basic model is very solid and has considered the right things. Expert E called this an important area needing more information.

The experts had some additional thoughts about needs in this area: intraspecies extrapolation studies (Expert B), species sensitivity data and human data (Expert C), and variations in exposure patterns (Expert E). Expert C commented that we need to know how animal models predict human response. Expert E believed that existing epidemiological studies are not very helpful and that a prospective, long-term, high-cost study would be more useful. Other experts expressed concerns about the value of existing epidemiological studies, but Expert A found the Seventh Day Adventist study (Euler et al., 1988) useful, and Expert C said that more studies like Lippmann's (Lippman et al., 1983) are needed.

3.2.3 Stratification in the Population at Risk

The experts apparently had no problem with including smokers in the populations at risk. Expert B said that it is all right to fold smokers in as part of the general population but did caution that they are at much greater risk than the rest of the population because they are already so compromised that additional stress is bound to make things worse. Expert A said that smoking should be a design factor in a controlled experiment; however, for this encoding, it can be assumed that smokers are randomly distributed throughout the population. It is not necessary to treat them as a separate group. Expert A noted that the same is true for chronic obstructive pulmonary disease and nutritional status. Expert B commented that diet, particularly vitamin E, makes a big difference at low exposure levels.

Expert A claimed that the populations of children and outdoor workers are not sufficiently different to warrant breaking them out separately but also noted that the consequences might be greater in children in terms of possibly having moderate as against mild lesions. Expert D commented that it is impossible to say whether children are more or less susceptible than adults. Expert F pointed out that most studies suggest no difference between adults and children, but certain studies (Lippmann et al., 1983; Spektor et al., 1988) suggest otherwise. Expert D believed it was a good idea to stratify on children versus adults; children are more resistant to some things, but they are going through a rapid growth phase and probably have a higher level of sensitivity to fibrotic changes than adults.

As for Los Angeles versus New York, Expert A stated that their monthly profiles are close enough to give rise to similar health effects and that their air quality patterns do not warrant breaking out the two areas. Expert B agreed. Expert F, however, believed that Los Angeles and New York should be considered separately because of differences in exposure patterns, with the very high peak values in Los Angeles (i.e., second-stage alerts) being very important.

In a more general vein, Expert A expressed concern with the term "responders," noting that the presence of sensitive airways may not correlate with the presence of lesions. Physiological response is based on airway response; morphological response is separate.

3.2.4 Sequence and Time Scale of Effects

Expert A noted that the time scale for centriacinar lesions is weeks, not months. Lesions have been seen in animals in six to eight weeks, and there is no reason to think matters are different in humans. However, Expert D said that, although acute effects occur quickly in both rats and humans, it takes approximately four to six months for chronic effects to develop in rats. Expert C went into more detail, stating that cellular injuries occur during the first 24 hours and that, by seven days, the cell population starts to differ and fibroblasts start to produce collagen. Beyond three months, the effects are irreversible.

Expert A went into the greatest detail with respect to exposure patterns, stating that the number of hours per day to induce an effect is not important. There is a threshold of 2-6 hours, but not much difference between 6 and 10 hours. An eight-hour average is fine. Expert A also claimed that we do not know enough to discriminate the effects of different exposure patterns; the subtleties of exposure patterns may be important, but all that is still a matter of conjecture. Expert C noted that the effects of continuous versus intermittent exposure differ only in degree,

not in pattern. However, Expert D claimed that the type of exposure pattern (at high exposures) clearly affects the damage that results.

In terms of the overall effect of peak versus cumulative exposure, there were different views expressed. On the whole, however, the experts seemed to believe that peak exposure is more important. For example, Expert E explicitly said that it is better to think about peak rather than cumulative exposure, and Expert F claimed that peaks are very important and that overall seasonal means or averages are less so. Expert C stated that ozone at low levels (less than 0.3 ppm) causes cellular (i.e., epithelial) damage by the cumulative dose reacting with tissue. In this case, the peaks in exposure do not really matter. At higher ozone levels, the peaks are important. Expert C also claimed that cumulative dose drives the response over a time frame of three weeks to three months, whereas peak concentration drives the acute response. Expert A emphasized that concentration, not time, is more important, claiming that the concept of concentration multiplied by time as a measure of effect is wrong.

The experts did not agree about the role of respites. Expert A said that having a respite is worse than not having one, in the sense that a whole new generation of sensitive cells develops during the respite. Expert D believed that respites may be important; the theory is that damage and misrepair over time are very important. Expert C stated that one can argue the role of respites both ways.

3.2.5 Degree of Repair

The degree of repair is related to the sequence and time scale of effects (Section 3.2.4). Expert A stated that, after a one-day exposure, the lungs would be back to "as normal as they will ever be" after 21 days, whereas Expert B judged this repair would take one week. For chronic effects, the experts were less optimistic about repair. Expert A noted that centriacinar lesions persist. Changes in the components of epithelial cells are not always reversible; once bronchiolarization (remodeling) takes place, such changes are irreversible. Expert B said that epithelial hyperplasia is seen after a three-month exposure and is not reversed six to nine months later; collagen deposition continues after exposure ceases, and the only thing that improves is the amount of inflammation. Expert C stated that destruction of alveoli and bronchiolarization do not reverse but that some cell changes in the epithelium do. Expert E's claim was weaker, that is, that a lesion can repair itself but that the degree of repair depends on the exposure concentration. Repair will not occur if the concentration is high enough, but, if the exposure level is low enough, the lungs can begin each ozone season in the same condition as at the beginning of the previous ozone season. Expert F commented that there is no reason to believe in adaptation for this phenomenon.

Misrepair was mentioned. For example, Expert C said that repair takes place but that it may be faulty. Expert D mentioned the theory that damage and misrepair over time are very important. Expert A said that repair occurs but questioned the degree of repair.

3.2.6 Interaction with Other Pollutants

The experts agreed that evidence of interaction is limited. As summarized by Expert A: "We know so little, it's difficult to say anything." Expert B noted that all pollutants have their effect (although data suggest that there is no synergy for sulfur dioxide and ozone) and that the

effects of different pollutants may be additive. A possible synergy mentioned by Expert D was sulfur oxides at low but not at high levels. Expert F was concerned about possible synergies between ozone and other pollutants. Expert F went on to state a concern about other oxidants (e.g., peroxyacetyl nitrate) that are more reactive than ozone. Expert E, on the other hand, was not convinced that synergism takes place.

Some experts said that, even if interactions with other pollutants occur, ozone plays the most important role. Expert D stated that, although other pollutants are clearly involved, ozone is the most important one. Expert C claimed that a small amount of synergism occurs between pollutants, but most of the injury is caused by ozone (i.e., "big bullet" as opposed to other "small bullets"). However, if ozone alters clearance, then other particles can become problematic. Expert E said that ozone is one of the more important pollutants for centriacinar lesions.

3.2.7 Health Significance

There were lively discussions about the possible health significance of ozone-induced centriacinar lesions. The possibility of such lesions leading to fibrosis was mentioned by Experts C and E. Most of the experts did not believe that such lesions lead to emphysema. Expert A stated that emphysema is not an endpoint of concern with ozone; Expert C claimed that ozone does not cause emphysema; and Expert E said that the formation of lesions apparently does not lead to emphysema or cancer. On the other hand, Expert F noted that the best correlate for functional decrement is emphysema, that centriacinar lesions probably produce centrilobular emphysema, and that such lesions certainly produce chronic bronchiolitis (i.e., small airway disease).

With respect to cancer, Expert C noted that ozone affects the ability to clear asbestos from the lung and thus could be viewed as potentiating the effects of another cocarcinogen or acting as a defense suppressor. Expert X* stated that, although the magnitude of the effect is unknown, air pollution may increase cancer metastasis and that it would be prudent for cancer patients to stay in clean air. However, as mentioned above, Expert E said that it does not appear that lesion formation leads to cancer. Expert A associated reduced clearance with increased susceptibility to infection, and Expert B mentioned that ozone exposure increases susceptibility to infection.

An effect thought to be related to ozone-induced lesions and viewed as important by the experts is accelerated depletion of lung function reserves with age. Expert F stated that one should be very concerned about centriacinar lesions, with the most important question being whether there is an inordinate depletion of lung reserve function. Expert C noted that chronic exposure causes stiffening (aging) of the lungs, and Expert B specifically mentioned that depletion of lung function reserves with age is accelerated by ozone exposure. Expert A, however, stated that centriacinar lesions are important but not directly linked to functional impairment.

The experts expressed more concern about the effects of centriacinar lesions on quality of life than on length of life. Expert E stated that quality of life (independent of lesions) could be affected. Expert D claimed that quality of life is restricted and that there are debilitative effects, but that it cannot be said whether longevity is affected. Expert C believed that quality

*Whenever a statement might disclose the identity of an expert, we attribute the statement to Expert X.

of life, rather than length of life, is the dominant effect, that we should worry about significant decrements in lung function later in life, and that other pulmonary diseases become more serious in the presence of ozone-induced lung injury. Expert B noted that homeostasis is affected by ozone exposure. Expert D concurred, saying that ozone could set up a change in homeostasis, particularly in susceptible individuals, and that over years of exposure that change should be cause for concern. Expert D also said that a person now able to perform normally may not be able to do so in 10 years as a result of living in an ozone nonattainment area.

4 SUMMARY AND CONCLUDING REMARKS

4.1 RISK ASSESSMENT PROCESS

This report summarizes the first phase of an assessment of chronic health risks associated with long-term exposure to ozone. The purpose of this assessment is to characterize current scientific judgment regarding the risk of lung injury or disease due to long-term ozone exposure. Mild and moderate lesions in the centriacinar region of the human lung were chosen as the health endpoints for which probabilistic exposure-response relationships were elicited from experts. The populations of interest were children aged 6 through 18 and all adult outdoor workers in Los Angeles and New York. Personal exposure conditions were expressed in terms of seasonal mean daily maximum eight-hour average concentrations of 0.025, 0.050, 0.075, and 0.100 ppm ozone. The experts were provided with data about characteristics of exposure patterns, such as distributions of personal daily maximum eight-hour exposures and personal and ambient daily peak exposures corresponding to each of the four seasonal mean values. Damage to the centriacinar region of the lung over 1 and 10 ozone seasons was considered.

The development of a carefully designed protocol was an important aspect of this project. The encoding protocol contained appropriate background material and supporting information, including data regarding exposure patterns and dosimetry results; definitions of health endpoints, population descriptors, and exposure conditions; factors to consider when making probability judgments; and factors relevant to judgments in the specific case of chronic health effects of ozone exposure. The protocol was pilot-tested and then used to elicit judgments from six experts selected because of their knowledge and familiarity with the health effects of ozone and because of our goal of having the group represent a wide range of respected scientific opinion on the questions of interest.

Quantitative judgments were encoded in the form of probabilities concerning exposure-response functions under particular exposure conditions. The encoded probabilities were to represent each expert's best judgment regarding what the population response rate (i.e., the proportion of the population showing the adverse effect – either mild or moderate ozone-induced centriacinar lesions) would be under each set of specified conditions (i.e., four ozone levels, two locations, two populations, and 1 or 10 seasons of ozone exposure). Qualitative judgments about various aspects of the chronic health effects of ozone exposure were also obtained from the experts, with particular emphasis on the factors to consider and on the long- and short-term health consequences of the lung damage resulting from long-term ozone exposure.

Quantitative and qualitative judgments were obtained from each of the six experts during the first round of encodings. The experts later met with the risk assessment team and EPA staff for a workshop devoted to discussing quantitative and qualitative judgments regarding the chronic health effects of long-term ozone exposure. A second round of encodings was then conducted with each of the experts so each could reconsider his or her judgments in light of the workshop discussions and the anonymous feedback resulting from review of the experts' judgments expressed in the first round of encodings.

4.2 RESULTS

4.2.1 Quantitative Results

The quantitative results consist of numerous sets of probabilistic judgments elicited from six experts about exposure-response relationships under a variety of conditions. Although other probabilities were obtained, the analysis focuses mainly on the median responses for each exposure-response relationship (i.e., on the median of an expert's distribution of the proportion of the population developing centriacinar lesions under the specified conditions) and the 0.05 and 0.95 fractiles of the distribution. The medians provide measures of central tendency, and the 0.05 and 0.95 fractiles form a central 90% CI that indicates an expert's uncertainty about the proportion of the population exhibiting either mild or moderate centriacinar lesions.

The experts differed about the details of specific exposure-response relationships. However, the results indicate that the experts agreed that ozone-induced centriacinar lesions would likely form under the stated conditions in at least some members of the populations of interest and that, in some cases, they would form in a substantial proportion of that population. For example, considering exposure for 10 seasons at a mean ozone concentration of 0.075 ppm, the judgments of five of the six experts implied a probability of at least 0.95 that 45% or more of the population of interest would develop mild centriacinar lesions. At higher ozone levels, some experts were almost sure that close to 100% would develop lesions. At lower ozone levels, on the other hand, some experts believed that there would be no response or low response rates. For example, for one season of exposure to ozone at 0.025 ppm, five out of six experts judged that median response rates would be at or very close to zero for moderate lesions. For mild lesions, the median response rates were judged to be zero for two experts, about 0.05 for two others, and much higher for the remaining two. At or above mean ozone exposure levels of 0.050 ppm, most experts agreed that chronic effects in the form of centriacinar lesions would likely occur in substantial numbers of people.

Certain consistent trends can be observed in the results. For example, response rates were higher for mild lesions than for moderate lesions. The magnitude of this difference varied, ranging from an average of 10% of the population at the low end to 50% at the high end. In a similar fashion, higher response rates were given for exposure over 10 seasons as against 1 season, although one expert did not differentiate between 1 and 10 seasons for mild lesions and a second expert had only very minor differences. At the high end, one expert had median shifts of 0.05-0.45 between 1 and 10 seasons. Finally, and predictably, the expected response rates increased as the mean ozone level increased, with some experts envisioning large jumps in response at certain points (e.g., moving from 0.050 ppm to 0.075 ppm) and others having a more linear (steady) increase in response rate over the four mean ozone concentrations used in the study.

The experts showed little inclination to stratify the populations of interest. Only one expert distinguished between children and outdoor workers, and only two experts distinguished between the two locations. Furthermore, even in those few situations, the differences in judgments were relatively small.

The median response rates varied from expert to expert, with one expert tending to have the highest values and another the lowest. The degree of uncertainty, as measured by the width of the 90% CIs, also varied among the experts and for different conditions. The degree of

uncertainty was sometimes extremely low, especially when an expert was reasonably sure that the response rate would be near zero or near 100%. At other times, the uncertainty was quite high, as in the case of a 90% CI from 22% to 93% of the population of interest. Despite such differences, a reasonable degree of overlap was evident among the 90% CIs for the same cases. Three of the experts overlapped in almost all cases and others overlapped frequently.

4.2.2 Qualitative Results

The experts agreed that the focus on centriacinar lesions was appropriate. Although they sometimes thought about the distinction between mild and moderate lesions in different ways, their reactions to the use of and definitions for mild and moderate lesions were basically favorable.

In considering the role animal data should play in making judgments about the effects of long-term ozone exposure on humans, certain types of animal studies (e.g., primate studies and studies involving long-term exposures and multiple endpoints) were viewed as more useful than others. The experts agreed that dosimetry modeling is very important, but they expressed concern about some of the values chosen for model parameters and the dosimetry results generated for this particular study. They saw a need for additional dosimetry modeling, animal studies, and epidemiological studies.

The experts noted the potential for differences between children and adults in the formation of ozone-induced lesions but believed that the evidence available to allow them to differentiate was limited and somewhat mixed. Similarly, four experts judged that the exposure patterns provided for Los Angeles and New York did not allow them to differentiate between the two locations in terms of the effects of long-term ozone exposure. Given that smokers were included in the populations at risk, some experts expressed concern about differential effects on smokers because of their status with respect to nutrition and chronic obstructive pulmonary disease.

The experts disagreed to some extent about the relative importance of peak versus cumulative exposure. One expert expressed a concern that not enough is known to discriminate between the effects of different exposure patterns. They could not agree about the role of respites; some experts seemed to view respites as beneficial, whereas others viewed them as making things worse. There were questions about the degree of repair and the possibility of misrepair. More information is needed on the effects of respites.

The evidence regarding the interaction of ozone with other pollutants and the relationships of such interactions to chronic health effects was judged to be limited. No specific synergies were the object of widespread concern among the experts, who seemed to agree that ozone plays a very important role in the formation of centriacinar lesions.

There were different points of view about the possible health significance of ozone-induced centriacinar lesions. Most of the experts believed that such lesions could lead to fibrosis or chronic bronchiolitis but probably not to emphysema. Some experts were concerned about an indirect relationship to cancer (e.g., through reduced ability to clear asbestos or other carcinogens from the lung). Many experts agreed that an important effect of ozone-induced centriacinar lesions is accelerated depletion of lung function reserves with age. This concern is related to how such lesions affect the quality as against the length of life. Significant decrements

in lung function late in life were believed to reduce quality of life by leading to changes in homeostasis and by rendering other pulmonary diseases more serious.

4.3 CONCLUDING REMARKS

The quantitative and qualitative results of the study are presented and discussed separately in this report. Part of the reason for this structure is that the discussions during the first encoding session and the day of the workshop did not focus specifically on the connections between the quantitative and qualitative judgments of the experts. Further, many of the qualitative comments in and of themselves did not shed much light on this issue. For example, Experts E and F tended to predict the lowest and highest response rates, respectively. Although both experts stressed peak as opposed to cumulative exposure, their other qualitative comments did not address possible explanations for their different response rates. In other instances, the connections were clearer. For example, Expert E (the only one not to differentiate between the effects of 1 and 10 seasons of ozone exposure, but only for mild lesions) claimed that each ozone season begins with the lungs in the same condition as at the beginning of the last period so long as the exposure is low enough. Expert C (the one whose probabilities imply substantial differences between 1 and 10 seasons) noted that destruction of alveoli and bronchiolarization do not reverse and that repair may be faulty. Also, certain of the qualitative comments explained the inability of some of the experts to discriminate between children and outdoor workers or between Los Angeles and New York.

The width of the CIs revealed a considerable degree of uncertainty on the part of the experts in many of the cases. This result is not surprising, given some of the uncertainties mentioned in the discussions. For example, with respect to dosimetry modeling and general extrapolation from animals to humans, Expert E expressed wariness of the results, stating that much uncertainty exists. Similarly, Expert C said that good predictive models are approximately five years away, and Expert A noted that the basic data needed to adjust parameters are still missing, particularly with respect to ventilation. Concern was also expressed about the information provided by epidemiological studies, with Expert B stating that such studies contain so much noise and multicollinearity that the ozone effect is hard to pick out. The experts also provided suggestions for future projects that could reduce the level of uncertainty.

Previous risk assessments for ozone have tended to focus on acute rather than chronic effects of exposure to pollutants. For acute effects, direct data were available on the relationship between exposure and the health endpoint in humans. For the chronic effects considered in this risk assessment, the data were indirect (e.g., from animal and epidemiological studies). The lack of direct data leads to considerable uncertainty and points to the importance of relating the indirect data to the questions of interest (e.g., relating animal data to implications for humans by means of dosimetry modeling).

Exposure conditions are more difficult to specify in chronic studies. Short-term exposures can be specified precisely, whereas long-term exposures involve difficult questions concerning exposure patterns over time. It is therefore important to determine what aspects of the exposure patterns are most important for the health endpoint of interest. For example, it may be important to know whether averages are sufficient, whether day-to-day changes matter, and whether peaks are important. Furthermore, in acute ozone studies, the health effects were readily observable (e.g., development of a cough or a reduction in ventilation rate), and the implications have been clearer (e.g., effects of a cough or a reduction in ventilation rate in the

short run). For a number of reasons, then, risk assessments involving chronic as against acute effects are much more complex. Experts are needed to sort out relationships in the absence of direct data and to suggest directions for future research. Assessments involving chronic effects can also be quite important. Questions concerning the long-term effects on quality and length of life are crucial.

The approach taken in this study builds on past risk assessments for criteria pollutants and represents the state of the art as procedures for risk assessments concerning health risks of pollutants continue to be developed and refined. Such procedures have been evolving over a decade of risk assessments conducted by OAQPS. Careful design of an encoding protocol and the ensuing encoding sessions and elicitation of probabilities regarding exposure-response relationships are not new (e.g., Whitfield and Wallsten, 1989).

What is new is bringing the experts, the risk assessment team, and EPA staff together for a risk assessment workshop that appears to have been a valuable addition for the following reasons.

- The workshop allowed the experts the opportunity to freely exchange viewpoints and perspectives about the scientific evidence and key issues affecting their judgments prior to the final encoding session. In principle and very likely in practice, this format results in more informed judgments in the final encoding session. At the same time, there was no pressure to adopt a consensus viewpoint for the sole sake of consensus. As a result of this exchange and discussion, one expert substantially changed his or her initial judgments.
- The workshop provided an opportunity for EPA staff to gain better insight into the reasonings and judgments of the experts regarding various issues (e.g., significance of effect, role of repair, influence of dosimetry modeling, and time sequence of effects) related to chronic ozone-induced lung injury.
- The workshop gave the experts the chance to offer feedback to EPA on the various elements of this phase of the risk assessment process, including the protocols, encoding sessions, and supporting analyses that were provided (i.e., exposure and dosimetry modeling).

The risk assessment team and EPA staff believe that the exchange of views at the workshop was very illuminating and valuable. Moreover, as noted in Section 2.4.3, the experts reacted very favorably to the workshop and were unanimous in stating that it was very informative and valuable to them. Although the experts are very busy, they said that the time at the workshop was well spent. We strongly recommend using such workshops in future risk assessments, whenever feasible.

The most obvious and concrete result of the risk assessment process is the set of probabilistic exposure-response judgments. This set represents the experts' current judgments about the degree of risk for the endpoints and conditions considered in the study. These quantitative results clearly show that chronic ozone effects in the form of centriacinar lesions are judged by the experts to be likely in at least some members of the populations of interest and, in some cases, in substantial proportions of those populations. Equally important are the qualitative comments made during the encoding sessions and at the workshop. Both types of

results serve to summarize the current state of scientific knowledge concerning the chronic effects of ozone exposure. They also provide new insights for the scientific research community about the future research needed to reduce uncertainties about the chronic health effects associated with exposure to ozone at elevated levels. This report serves to communicate those insights. The experts participating in the risk assessment have already benefited in this manner from the risk assessment process. For example, one expert commented that the encoding process and the discussions at the workshop had led to an entirely new way of thinking about research and about the adverse effects associated with ozone exposure. Much research, by its very nature, focuses on small parts of the overall problem of health risks associated with ozone. The risk assessment process enables researchers and others to step back and think about the bigger picture.

This report presents the results of the first phase of the chronic lung injury risk assessment for ozone. In the second phase, OAQPS plans to combine the results of this assessment with exposure estimates from the probabilistic NAAQS Exposure Model for Ozone (McCurdy et al., 1991) to generate risk estimates for several urban areas, including Los Angeles and New York.

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APPENDIX A
ENCODING PROTOCOL

APPENDIX A

ENCODING PROTOCOL

Appendix A is the protocol used for the encoding sessions. There are nine sections: introduction; centriacinar lesions; exposure conditions; population at risk; factors to consider; health significance; factors to keep in mind when making probability judgments; session two: discussion of judgments, health significance, and research needs; and references.

A.1 INTRODUCTION

The U.S. Environmental Protection Agency (EPA) is charged by the Clean Air Act with setting and revising primary and secondary national ambient air quality standards (NAAQS) for selected pollutants. The primary standards are to be set at levels sufficient to protect public health with an adequate margin of safety on the basis of the scientific evidence presented and reviewed in criteria documents. In support of the current review of the ozone NAAQS, EPA has prepared a new Criteria Document entitled *Air Quality Criteria for Ozone and Other Photochemical Oxidants* (EPA, 1986), a Criteria Document Supplement (EPA, 1990), and an Office of Air Quality Planning and Standards (OAQPS) Staff Paper (EPA, 1989). These documents present the scientific evidence from which the most susceptible populations can be determined and from which various adverse health effects can be identified. The Criteria Document and Supplement summarize and evaluate the human clinical, epidemiological, and animal toxicological evidence with regard to the physiological and adverse health effects of ozone and other photochemical oxidants, and therefore represent our current knowledge about their effects based on the peer-reviewed scientific literature. The Staff Paper interprets material in the Criteria Document and makes recommendations to the EPA Administrator.

During the review process, the issue has been raised as to whether repeated or long-term exposure to ozone at levels observed in areas such as southern California or the Northeast leads to chronic effects in the form of irreversible lung injury and/or lung disease. This issue has also surfaced in deliberations of the U.S. Congress and the Executive Branch over the form of the revisions to the Clean Air Act Amendments with respect to the ozone nonattainment policy. The purpose of this project is to provide a better characterization of scientific judgment regarding the risk of lung injury and/or disease due to long-term ozone exposure in places such as southern California and the Northeast. The results of this project, both qualitative and quantitative judgments, will not be used in the ongoing review of the ozone primary ambient air quality standard. They will be used to inform policymakers and the public about the possible health implications of long-term exposure to ozone, based on the judgment of scientists most familiar with research on the chronic effects of ozone and scientists most familiar with the development of chronic lung injury or disease due to environmental factors.

Because the risk estimates that EPA seeks are based in part on exposure-response relationships that are uncertain, it is necessary for the purpose of risk assessment to make probability judgments about relevant exposure-response functions, based on the available evidence. Obtaining health risk estimates then involves combining air quality or exposure estimates with exposure-response probability assessments.

The problem of judging exposure-response relationships frequently is similar to that which exists in clinical medicine when there are insufficient data that bear precisely on the patient's problem. In that case, it is necessary to use scientific judgment to make the best assessment of the patient's condition, given the data at hand. Here, too, it is necessary to use scientific judgment to extrapolate from the available data. The extrapolation is not certain and, therefore, we will aid you in representing your opinion probabilistically. The probabilistic representation of your judgments that we obtain will be used only with your full agreement that it accurately represents your best judgments.

Furthermore, since the extrapolation depends on one's interpretation of the literature, different people will have different judgments. For the health endpoint considered here, we intend to obtain the judgments of experts who represent a range of scientific opinions. The model for estimating risks will not merge these judgments into a single average judgment, but rather will estimate a range of risks based on the range of judgments. By eliciting your knowledge in a structured manner, not only will we be able to show policymakers a range of risk estimates based on a range of judgments from those most familiar with the state of knowledge in this field, but we will also be able to show some of the sources of any disagreements. Indeed, a side benefit of the encoding may be to help identify the sources of greatest disagreement.

Based on the evidence in the Criteria Document and Supplement, various populations have been identified as being potentially at risk for adverse effects of ozone. Several potentially adverse health effects have been identified, and we would like to assess exposure-response functions for the one discussed below.

A.2 CENTRIACINAR LESIONS

We would like to represent in probabilistic form your judgments about the location and shape of several exposure-response functions for accumulated ozone-induced human lung injury in the form of centriacinar lesions, as defined below. Because available data do not fully define these functions, it is important that we obtain judgments about them from you and other experts. If the population, the exposure conditions, and the physiological effects were all precisely defined, then in principle such functions could be empirically established. We would like your best judgment about what these functions might look like if the data could be collected. We are also interested in the reasoning behind your judgments.

Animal studies discussed in Chapter 10 of the Criteria Document suggest that ozone exposure at sufficiently high concentrations over a prolonged enough period results in lung structural changes. Among the possible effects of prolonged exposure may be distal airway narrowing (i.e., thickened respiratory bronchiole walls); remodeling of the centriacinar airways; and thickening of the interalveolar septa (due in part to increased collagen and epithelial thickness).

We wish to elicit your judgments about exposure-response curves for two different levels of centriacinar lesions in humans. For the purposes of this encoding, we define mild centriacinar lesions as those detectable only by highly sensitive techniques and quantitative analysis. These procedures include, but are not limited to, morphometric techniques, special stains, and electron microscopy. We define moderate centriacinar lesions as those detectable by qualitative assessment using light microscopy but not necessarily by gross techniques.

We will elicit probability judgments from you about the shape and location of the exposure-response curve for selected subpopulations potentially at risk to ozone exposure. (We define those subpopulations later in this protocol.) Numerous animal studies are summarized in the Criteria Document and in the Supplement. You may wish to refer to these materials as you reflect on the possibility and potential magnitude of responses in humans. We recognize that respiratory tract structural and other differences exist among animal species, resulting in interspecies differences in the amount of ozone reaching lung tissues, given common exposures, and that there is limited information available on differences in species sensitivity to equivalent delivered ozone doses. We further recognize that a considerable degree of extrapolation is required to infer the desired, but unknown, exposure-response curves for humans from available animal studies.

For obvious ethical reasons, it is not possible to conduct the experiments that would be required to measure these curves in humans. Consequently, despite the unavoidable uncertainty in doing so, animal results must be extrapolated to humans to assess the risk of long-term exposure to elevated ozone concentrations. We believe that you and your colleagues involved in this encoding, as recognized experts, are the people most qualified to render the judgments required for such extrapolation.

You may feel a lesser or greater amount of certainty in making the required judgments. The purpose of our efforts is to obtain your judgments probabilistically, in a fashion that accurately reflects the degree of your certainty. Where you are more certain, the uncertainty bounds in the curves we elicit from you will be tighter. Where you are more uncertain, they will be broader.

To assist you in preparing for the encoding, we will provide you with copies of the Criteria Document and Criteria Document Supplement, as well as any of the referenced papers that you may request. Also, because of its very recent nature and possible relevance, we are including in the material sent to you a summary of recent dosimetry predictions for a 13-year-old child and an outdoor worker based on actual activity and air quality patterns. When we begin the encoding, we will discuss the animal studies and dosimetry predictions with you in order to obtain your opinions regarding the degree to which you believe they are useful in estimating the desired human exposure-response curves.

A.3 EXPOSURE CONDITIONS

We now define the exposure conditions that we would like you to assume when making judgments about the relationship of ozone exposure to centriacinar lesions. Centriacinar lesions might take a long period to develop (months or years). Also, their incidence could be most associated with high chronic concentration levels averaged over a long period of time, with the accumulated effect of multiple, repeated peak exposures, or with both. Furthermore, some lung structural changes might be irreversible, while others might be all or partially reversible.

We will encode your judgments about the relationship between the incidence of centriacinar damage and ozone exposure over each of two time periods: a single ozone season and 10 ozone seasons. The concentration levels that we will specify will be seasonal averages of the daily maximum eight-hour averages. We will encode your judgments about population response rates at a series of seasonal mean daily maximum eight-hour average ozone concentrations measured in parts per million (ppm) corresponding to the current range of exposures.

In further specifying the exposure conditions, we would like to ask that you assume the following:

Pattern of Exposure. Although we will be asking you to assume specific mean daily maximum eight-hour average concentrations over 1 to 10 ozone seasons, the actual hour-by-hour exposure patterns are made up of the short-term air concentrations encountered during a complex sequence of movements from one indoor or outdoor environment to another. Indoor ozone concentrations are usually much lower than those outdoors, and outdoor concentrations vary diurnally and from one day to the next. We recognize that a number of possible sequences of hourly concentrations are possible, many of which could be associated with the same daily maximum eight-hour average concentration.

To aid you in conceptualizing the relationship between hour-to-hour fluctuations in ozone exposure over a season and a resulting mean daily maximum eight-hour average concentration, we have prepared frequency distributions of one-hour average exposures for seasons and activity patterns that yield specific mean daily maximum eight-hour averages. We have also prepared frequency distributions of the daily maximum eight-hour averages corresponding to the particular mean value over a season.

Some of these distributions were generated from the ambient exposure data for 1983 (in the Los Angeles and New York City consolidated metropolitan statistical areas [CMSAs]) in conjunction with activity patterns for 6- to 18-year-old children and for outdoor workers. The remainder of the distributions were obtained by using the same activity patterns, but adjusting the ambient exposure by applying models to the 1983 data. In addition to these frequency distributions, we have data concerning other characteristics of the exposure, should you want them.

The effect of ozone on centriacinar lesions depends on the dose at the site in the lung rather than on the exposure at the nose and mouth. Actual human tissue dose as a function of exposure is unknown, but has been modeled by using dosimetric techniques. To aid you in your judgments, we have dosimetric results for a rat exposed under a specific laboratory protocol, as well as for a 13-year-old and an outdoor worker under the same protocol, given their activity pattern. In addition, we have results for a 13-year-old and an outdoor worker for a single 12-hour period based on Los Angeles and New Jersey air quality patterns.

Exposure History. Assume the existence of a respite period corresponding to the time between ozone seasons in each location.

Ambient Conditions. Assume temperature and relative humidity conditions to be those that typically occur during the ozone season for each location.

Other Pollutants. Assume that the concentration distributions of other pollutants, such as nitrogen dioxide, sulfur dioxide, acid aerosols, and particulate matter, are as they would be expected to be on a typical day during the ozone season.

A.4 POPULATION AT RISK

The Criteria Document identifies three groups as potentially at risk for adverse health effects due to ozone: those persons with preexisting respiratory disease, those who for currently unknown reasons are "responders" (i.e., who are especially sensitive to ozone), and those whose activities out of doors result in increases in lung ventilation. However, for the purposes of this encoding, we define the populations of interest as all children aged 6 through 18 and all adult outdoor workers. We will consider these populations in both the Los Angeles and New York City CMSAs.

The populations of interest include people within a broad age span, those with and without respiratory problems and allergies, smokers and nonsmokers, and those of both sexes. If you think that any of these factors affects the exposure-response functions, we may have to consider subpopulations stratified according to one or more of them. For example, you may wish to think of normal healthy adult workers separately from those with chronic obstructive lung disease. However, in considering whether to stratify, keep in mind that we are now concerned only with the probability of an effect occurring, not with the degree of adversity of the effect. For example, a given decrement in lung function may be more serious for an individual with already reduced lung function than for a normal healthy person, but if the probability of occurrence of the decrement is the same for both under the same exposure conditions, the two groups can be represented by a single exposure-response relationship.

Assume the distributions of chronic obstructive lung diseases, colds, allergies, etc., that you believe exist in the populations of interest. If you believe that any aspect of nutritional status is important in determining ozone responsiveness, then assume that factor is distributed as you think it is in the population of interest.

Level of activity (light, moderate, heavy, and very heavy) is important in determining the effect of a given ozone exposure. For our purposes here, we are concerned with long-term exposure, which makes it difficult to integrate the influence of activity periods. Therefore, we ask you to assume that the distribution, intensity, and timing of activity are those typically occurring in the populations of interest during the ozone season.

A.5 FACTORS TO CONSIDER

In responding to the questions we will ask, please make use of the relevant studies summarized in the Criteria Document and Supplement, as well as all other information you may have and your interpretations of this information. In order to help you bring to mind the relevant evidence so that you may consider it systematically, and also in order to help us to interpret your judgments, we would like to ask you to discuss briefly your interpretation of various aspects of the literature.

General Literature. The consideration of lung structural changes in humans as a result of exposure to ozone is made difficult by the lack of directly relevant data involving humans. The large body of evidence from animal studies demonstrates that chronic exposures to ozone can cause changes in lung structure. Can you tell us which of these studies you find most useful and why, in terms of their implications for the existence of and the magnitude of similar effects in humans? In addition, are any recent epidemiological studies relevant?

Extrapolation of Animal Studies. The basic mechanisms of action associated with ozone-induced pulmonary inflammation and lung structural changes observed in animals may be similar to those in humans. However, differences in lung structure and biological response will inevitably cause differences in dosimetry and species sensitivity. Can you indicate what sort of available information about these factors is helpful to you in attempting to extrapolate from animal studies to humans?

Sequence of Response. What are your thoughts about the various stages leading from exposure to response? First, consider the relationship between exposure, eventual dose at the tissue level, and resulting lung structural changes. What sorts of alterations in lung structure do you associate with ozone exposure? What implications might these changes have for humans?

Time Scale of Effects. Some animal studies indicate that centriacinar lesions can appear within a relatively short time period. What would you expect to be the case for humans? At a fixed concentration level, what would you expect the time progression of inflammation and resulting terminal airway and alveolar changes to be, as the exposure duration increases?

Degree of Repair. Animal studies also indicate that some degree of damage repair, or adaptation, may take place during continued exposure. Do you agree? Would you expect this to be the case with humans? If so, what do you think the repair mechanisms might be? To what extent would you expect lung structural changes to be repaired during continuing exposure? During postexposure periods?

Effect of Time-Varying Exposure Concentrations. Some animal studies have been conducted using constant ozone exposure levels, while others have used diurnally varying or intermittent concentration levels. Given the same average value, do you believe the pattern of exposure affects results? Can you comment on the potential cumulative effect of repeated exposures?

Interaction with Other Pollutants. Some animal studies have reported a synergism between ozone and ammonium sulfate or sulfuric acid droplets. The concentrations of the copollutants with ozone, however, have been at concentrations higher than those observed in ambient air. Do you think that such synergisms are significant for humans at ambient concentration levels, and why? If so, what copollutants do you think are likely to interact significantly with ozone to increase its effect on human health?

A.6 HEALTH SIGNIFICANCE

Please discuss with us what you consider to be both the long- and short-term health consequences of the lung damage addressed here. Is it significant in and of itself? At what point would you label the damage as fibrosis? Is it a marker of other adverse consequences? If so, what are they?

A.7 FACTORS TO KEEP IN MIND WHEN MAKING PROBABILITY JUDGMENTS

Uncertainty is usually associated with conclusions that we draw from research and more generally in our everyday thinking. Many sources contribute to this uncertainty, and it is difficult for most people to consider and integrate them all. When an expert is asked to make probability judgments on socially important matters, it is particularly important that he or she consider the relevant evidence in a systematic and effective manner and provide judgments that represent his or her opinions well.

Experimental psychologists and decision analysts have amassed a considerable amount of data concerning the way people form and express probabilistic judgments. The evidence suggests that, when considering large amounts of complex information, most people use heuristics (i.e., simplifying rules) and demonstrate certain cognitive biases (i.e., systematic distortions of thought). The purpose of this section is to make you aware of these biases and heuristics. We will first review the most widespread biases and heuristics, and then offer some suggestions to help you mitigate their effects.

A.7.1 Sequential Consideration of Information

Generally, the order in which evidence is considered influences the final judgment, although logically that should not be the case. Of necessity, pieces of information are considered one by one in a sequential fashion. However, those considered first and last tend to dominate judgment. In part, initial information has undue influence because it provides the framework that subsequent information is then tailored to fit. For example, people usually search for evidence to confirm their initial hypotheses; they rarely look for evidence that weighs against them. The latter evidence has an undue effect simply because it is fresher in memory.

Related to these sequential effects is the phenomenon of "anchoring and adjustment." Based on early partial information, one forms an initial probability estimate regarding the event in question. This anchor judgment is then adjusted as subsequent information is considered. Such adjustments tend to be too small. In other words, too little weight is attached to information considered subsequent to the formation of the initial judgment.

A.7.2 Effects of Memory on Judgment

It is difficult for most people to conceptualize and make judgments about large, abstract universes or populations. A natural tendency is to recall specific members and then to consider them as representative of the population as a whole. However, the specific instances often are recalled precisely because they stand out in some way, such as being familiar, unusual, especially concrete, or of personal significance. Unfortunately, the specific characteristics of these singular examples are then attributed, often incorrectly, to all the members of the population of interest. Moreover, these memory effects are often combined with the sequential phenomena discussed earlier. For example, in considering the evidence regarding the exposure-response curve of a particular pollutant, you might naturally think first of a study you recently read or one that was unusual and therefore stands out. The tendency might then be to treat the recalled studies as typical of the population of relevant research and ignore important differences among studies. Subsequent attempts to recall information could result in thinking primarily of evidence consistent with the initial items considered.

A.7.3 Estimating Reliability of Information

People tend to overestimate the reliability of information, ignoring factors such as sampling error and imprecision of measurement. Rather, they summarize evidence in terms of simple and definite conclusions, which causes them to be overconfident in their judgments. This tendency is stronger when one has a considerable amount of intellectual and/or personal involvement in a particular field. In such cases, information is often interpreted in a way that is consistent with one's beliefs and expectations, results are overgeneralized, and contradictory evidence is ignored or underestimated.

A.7.4 Relation between Event Importance and Probability

Sometimes the importance of events, or their possible costs or benefits, influences judgments about the certainty of the events when, rationally, importance should not affect probability. In other words, one's attitudes toward risk tend to affect one's ability to make accurate probability judgments. For example, many physicians tend to overestimate the probability of very severe diseases because they feel it is important to detect and treat them; similarly, many smokers underestimate the probability of adverse consequences of smoking because they feel that the odds do not apply to themselves personally.

A.7.5 Assessment of Probabilities

Another limitation is related to one's ability to discriminate between levels of uncertainty and to use appropriate criteria of discrimination for different ranges of probability. One result is that people tend to assess both extreme and midrange probabilities in the same fashion, usually doing a poor job in the extremes. It is important to realize that the closer to the extremes (either 0 or 1) that one is assessing probabilities, the greater the impact of small changes. It helps here to think in terms of odds as well as probabilities. Thus, for example, changing a probability by 0.009 from 0.510 to 0.501 leaves the odds almost unchanged, but the same change from 0.999 to 0.990 changes the odds by a factor of about 10, from 999:1 to 99:1.

A.7.6 Recommendations

Although extensive and careful training would be necessary to eliminate all the problems mentioned above, some relatively simple suggestions can help minimize them. Most important is to be aware of natural cognitive biases and to try consciously to avoid them.

To avoid sequential effects, keep in mind that the order in which you think of information should not influence your final judgment. It may be helpful to actually note on paper the important facts you are considering and then to reconsider them in two or more sequences, checking the consistency of your judgments. Try to keep an open mind until you have gone through all the evidence, and don't let the early information you consider sway you more than is appropriate.

To avoid adverse memory effects, define various classes of information that you deem relevant, and then search your memory for examples of each. Don't restrict your thinking only to items that stand out for specific reasons. Make a special attempt to consider conflicting

evidence and to think of data that may be inconsistent with a particular theory. Also, be careful to concentrate on the given probability judgment, and do not let your own values (how you would make the decision yourself) affect those judgments.

To accurately estimate the reliability of information, pay attention to such matters as sample size and the power of the statistical tests. Keep in mind that data are probabilistic in nature, subject to elements of random error, imprecise measurements, and subjective evaluation and interpretation. In addition, the farther one must extrapolate, or generalize, from a particular study to a situation of interest, the less reliable is the conclusion and the less certainty should be attributed to it. Rely more heavily on information that you consider more reliable, but do not treat it as "absolute truth."

Keep in mind that the importance of an event or an outcome should not influence its judged probability. It is rational to let the costliness or severity of outcome influence the point at which action is taken with respect to it, but not the judgment that is made about the outcome's likelihood. Finally, in making probability judgments, think primarily in terms of the measure (probability or odds) with which you feel more comfortable, but sometimes translate to the alternative scale, or even to measures of other events (e.g., the probability of the event not happening). When estimating very small or very large likelihoods, it is usually best to think in terms of odds, which are unbounded, instead of probabilities, which are bounded. For example, one can more easily conceptualize odds of 1:199 than a probability of 0.005.

A.8 SESSION TWO: DISCUSSION OF JUDGMENTS, HEALTH SIGNIFICANCE, AND RESEARCH NEEDS

It is currently planned that, at a subsequent meeting of the participating experts and others, we will show you the encoded judgments of all the experts. Anonymity will be preserved in the presentation of these results; individuals will be identified only by code number or letter, not by name. The purpose of the meeting is to discuss the reasoning that led individuals to their particular judgments, the health consequences of chronic lung injury, and the research needed to resolve the identified uncertainties. Please note that our purpose here is not to cause you to alter your judgments, but rather to obtain as full an understanding as possible of the current state of knowledge regarding chronic ozone effects. At the end of the meeting, we will meet individually with you to reconsider your encoded judgments and to make any changes you wish.

A.9 APPENDIX A REFERENCES

EPA, 1986, *Air Quality Criteria for Ozone and Other Photochemical Oxidants*, U.S. Environmental Protection Agency Report EPA-600/8-84/020a to 020e. (For copies, contact U.S. Environmental Protection Agency, Center for Environmental Research Information, USEPA/ORD Publications, 26 West St. Clair, Cincinnati, Ohio 45268, (513) 569-7652.)

EPA, 1988, *Summary of Selected New Information on Effects of Ozone on Health and Vegetation: Draft Supplement to Air Quality Criteria for Ozone and Other Photochemical Oxidants, CASAC Review Draft*, Report EPA/600/8-88/105A. (For copies, contact U.S. Environmental Protection Agency, Center for Environmental Research Information, USEPA/ORD Publications, 26 West St. Clair, Cincinnati, Ohio 45268, (513) 569-7652.)

EPA, 1989, *Review of the National Ambient Air Quality Standards for Ozone: Preliminary Assessment of Scientific and Technical Information*, draft staff paper. (For copies, contact David McKee, U.S. Environmental Protection Agency, OAQPS, MD-12, Research Triangle Park, N.C. 27711, (919) 541-5288.)

APPENDIX B

**EXAMPLE OF THE OZONE AIR QUALITY AND EXPOSURE
INFORMATION PROVIDED TO THE EXPERTS**

APPENDIX B

EXAMPLE OF THE OZONE AIR QUALITY AND EXPOSURE
INFORMATION PROVIDED TO THE EXPERTS

This appendix briefly describes the logic behind and development of the exposure information given to the experts. Included is a figure typical of those provided. A complete description and full results are presented in Rosenbaum and Hayes (1990).

As mentioned in Section 2.1, we decided during the protocol development phase to use seasonal mean daily maximum eight-hour average concentrations of personal exposure as the measure of ozone exposure. At the time of the encoding sessions, there were two prevalent schools of thought about exposure "patterns" that cause lung injury. One holds that cumulative dose is the most important consideration; the other holds that peak exposure (i.e., largest dose) is the most important consideration.

To accommodate these two points of view, we provided the experts with simulated personal exposure estimates, that is, exposure levels that individual children or adult outdoor workers might encounter during the ozone season. These estimates were developed by using the Personal Air Quality Model (PAQM) described in Hayes (1989). PAQM simulates indoor and outdoor exposure, taking into account individual hourly activity profiles based on actual time-budget data for weekdays (Roddin, Ellis, and Siddiquee, 1979) and weekends (Johnson and Paul, 1983). The activity profile assigns an individual for each hour to one of six microenvironments: outdoors; inside a vehicle; school (building not weatherized); office (building not weatherized); other indoor locations, including home (windows closed and building not weatherized); and other indoor locations, including home (windows open during daytime in warm weather).

Figure B.1 shows the type of information we provided. There are three histograms: one for personal daily maximum eight-hour average exposure (to address the cumulative dose school of thought); one for daily maximum personal exposure (to address the peak exposure school of thought); and one for daily maximum ambient conditions (to show the air quality from which the personal exposure was derived).¹ The ambient conditions, which are based on design monitor data, are adjusted by PAQM to obtain a desired mean daily maximum eight-hour average personal exposure level (0.075 ppm in the case shown). Because we encoded judgments at four levels of personal exposure (0.025, 0.050, 0.075, and 0.100 ppm) for children and adult outdoor workers in two geographic locations, this figure is only 1 of the 16 figures of this type that we provided. As might be expected, personal exposure levels are lower than ambient levels.

In addition to the simulated data sets depicted in the aforementioned 16 figures, means and frequency distributions of monitored ambient data for Los Angeles and New York and the PAQM time series derived from those data were also presented to the experts as background information. The monitoring data were analyzed for episode duration and respite between episodes as well. The figures that present this background material are also included in Rosenbaum and Hayes (1990).

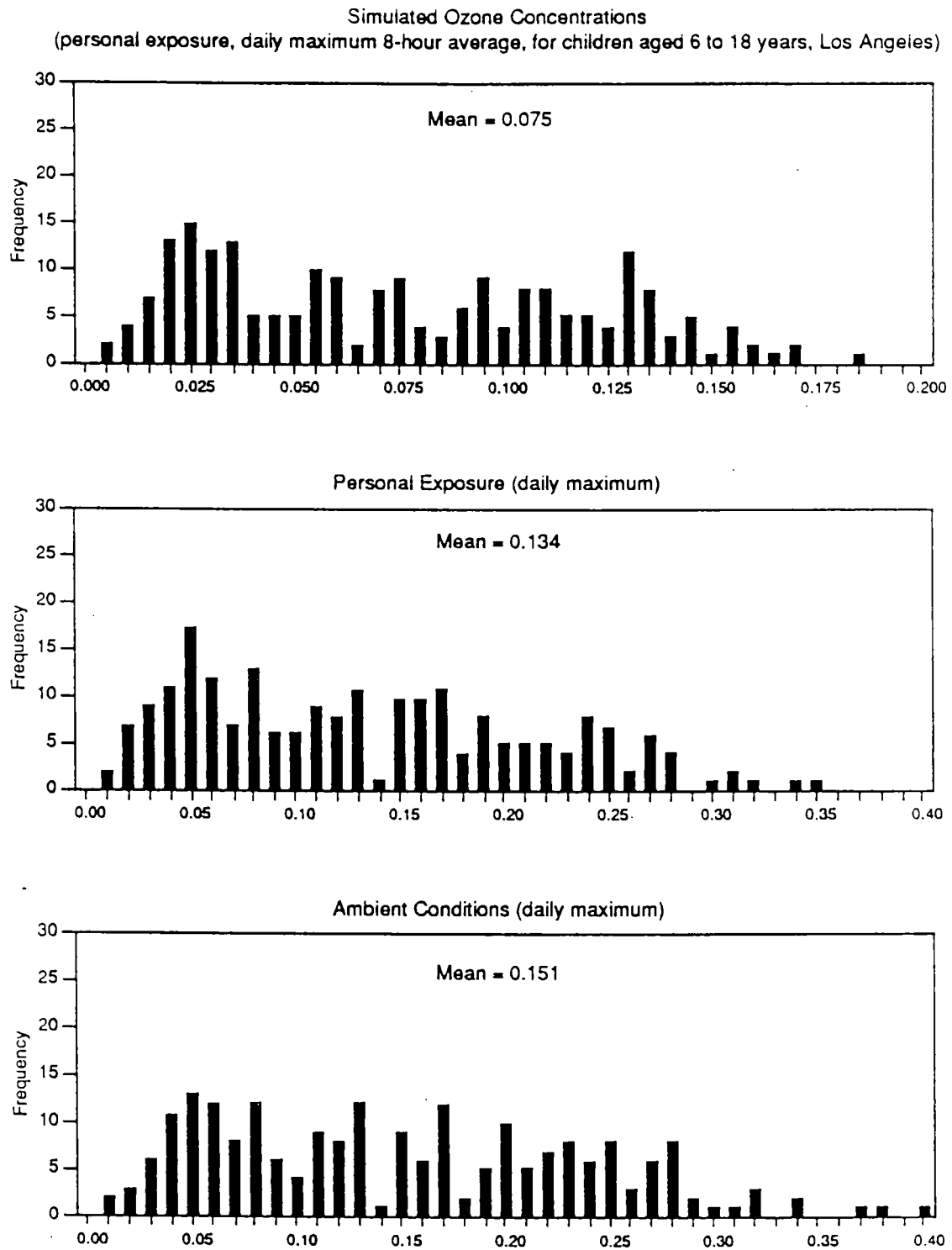


FIGURE B.1 Example of the Exposure Information Provided to the Experts

APPENDIX B REFERENCES

Hayes, S.R., 1989, *Estimating the Effect of Being Indoors on Total Personal Exposure to Outdoor Air Pollution*, J. Air Pollution Control Association, 39(11):1453-1461.

Johnson, T., and R.A. Paul, 1983, *The NAAQS Exposure Model (NEM) and Its Application to Carbon Monoxide*, U.S. Environmental Protection Agency Report EPA-450/5-83-003. (For copies, contact Thomas R. McCurdy, U.S. Environmental Protection Agency, OAQPS, MD-12, Research Triangle Park, N.C. 27711, (919) 541-5288.)

Roddin, M.F., H.T. Ellis, and M.W. Siddiquee, 1979, *Background Data for Human Activity Patterns, Volumes 1 and 2*, draft report prepared for U.S. Environmental Protection Agency, Research Triangle Park, N.C. (For copies, Thomas R. McCurdy, U.S. Environmental Protection Agency, OAQPS, MD-12, Research Triangle Park, N.C. 27711, (919) 541-5288.)

Rosenbaum, A.S., and S.R. Hayes, 1990, *Patterns of Personal Exposure to Ozone in Los Angeles and New York*, draft report prepared for U.S. Environmental Protection Agency. (For copies, contact Harvey M. Richmond, U.S. Environmental Protection Agency, OAQPS, MD-12, Research Triangle Park, N.C. 27711, (919) 541-5271.)

APPENDIX C
PROBABILITY JUDGMENTS

APPENDIX C

PROBABILITY JUDGMENTS

The probability judgments are presented in Table C.1. The table is organized so that each expert, lesion-type, city, population, and number-of-ozone-seasons combination is listed, beginning with Expert A and continuing alphabetically through Expert F. Sixteen combinations are possible, and each combination is referred to as a case. The table is explained below, with the judgments of Expert A used as an example.

Expert A did not distinguish between children and outdoor workers or between Los Angeles and New York. Thus, 4 sets of judgments by Expert A cover the 16 possible combinations. Each set of judgments is identified with a code. The first of these, denoted by the code AIBB1, covers four of the cases. After the code, a short description of the meaning of the code is given. Each set of judgments consists of from one to four probability distributions over response rate that are conditional on ozone concentration (0.025, 0.050, 0.075, or 0.100 ppm). The table then lists response rates (under the columns labeled R) and corresponding cumulative probabilities (under the columns labeled F). Because Expert A provided a probability distribution for each ozone concentration, four distributions are listed. Eight points were encoded for the first distribution (0.025 ppm). For example, the probability that the response rate is ≤ 0.3 is 0.35, the probability that the response rate is ≤ 0.65 is 0.85, and so forth.

TABLE C.1 Encoded Judgments about Population Response Rates for Ozone-Induced Lesions in the Centriacinar Region of the Human Lung

Response Rate and Cumulative Probability, by Ozone Concentration								
Code	0.025 ppm		0.050 ppm		0.075 ppm		0.100 ppm	
	R ^a	F ^b	R	F	R	F	R	F
AIBB1:	Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, 1 Ozone Season							
	0.15	0.01	0.25	0.01	0.4	0.01	0.5	0.01
	0.22	0.1	0.33	0.1	0.6	0.35	0.6	0.15
	0.3	0.35	0.4	0.29	0.65	0.5	0.75	0.5
	0.35	0.5	0.5	0.5	0.9	0.95	0.9	0.9
	0.45	0.69	0.78	0.81	0.93	0.99	0.95	0.99
	0.55	0.78	0.9	0.99				
	0.65	0.85						
	0.75	0.99						
AIBB10:	Expert A, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, 10 Ozone Seasons							
	0.3	0.01	0.4	0.01	0.65	0.01	0.9	0.01
	0.35	0.1	0.55	0.15	0.75	0.25	0.97	0.5
	0.45	0.35	0.75	0.5	0.85	0.5	0.999	0.99
	0.5	0.5	0.8	0.7	0.95	0.75		
	0.55	0.69	0.9	0.99	0.99	0.99		
	0.65	0.81						
	0.75	0.89						
	0.85	0.99						
A1BB1:	Expert A, Moderate Lesions, Los Angeles and New York Children and Outdoor Workers, 1 Ozone Season							
	0.01	0.01	0.05	0.01	0.15	0.01	0.35	0.01
	0.05	0.1	0.15	0.08	0.29	0.14	0.45	0.2
	0.11	0.35	0.3	0.29	0.43	0.32	0.55	0.39
	0.14	0.5	0.4	0.5	0.5	0.5	0.625	0.5
	0.2	0.67	0.53	0.81	0.67	0.7	0.75	0.66
	0.3	0.9	0.6	0.99	0.75	0.99	0.95	0.99
	0.5	0.99						

TABLE C.1 (Cont'd)

Response Rate and Cumulative Probability, by Ozone Concentration								
Code	0.025 ppm		0.050 ppm		0.075 ppm		0.100 ppm	
	R	F	R	F	R	F	R	F
A0BB10:	Expert A, Moderate Lesions, Los Angeles and New York, Children and Outdoor Workers, 10 Ozone Seasons							
	0.05	0.01	0.2	0.01	0.5	0.01	0.6	0.01
	0.1	0.1	0.3	0.08	0.6	0.14	0.7	0.1
	0.145	0.25	0.45	0.29	0.7	0.32	0.875	0.5
	0.22	0.5	0.55	0.5	0.75	0.5	0.95	0.91
	0.3	0.69	0.65	0.81	0.85	0.7		
	0.4	0.84	0.7	0.99	0.9	0.99		
	0.5	0.92						
	0.6	0.99						
B1BC1:	Expert B, Mild Lesions, Los Angeles and New York, Children, 1 Ozone Season							
	0.01	0.13	0.01	0.1	0.6	0.01	0.96	0.01
	0.04	0.5	0.05	0.5	0.63	0.13	0.96	0.1
	0.06	0.83	0.1	0.75	0.66	0.22	0.98	0.3
	0.1	0.999	0.2	0.95	0.73	0.45	0.999	0.5
			0.25	0.99	0.75	0.5		
					0.83	0.62		
					0.85	0.99		
B1BC10:	Expert B, Mild Lesions, Los Angeles and New York, Children, 10 Ozone Seasons							
	0.16	0.13	0.16	0.1	0.8	0.01	0.99	0.001
	0.19	0.5	0.2	0.5	0.82	0.13	0.999	0.999
	0.21	0.83	0.25	0.75	0.84	0.22		
	0.25	0.999	0.35	0.95	0.87	0.45		
			0.4	0.99	0.89	0.5		
					0.96	0.62		
					0.98	0.99		

TABLE C.1 (Cont'd)

Response Rate and Cumulative Probability, by Ozone Concentration								
Code	0.025 ppm		0.050 ppm		0.075 ppm		0.100 ppm	
	R	F	R	F	R	F	R	F
BIBW1:	Expert B, Mild Lesions, Los Angeles and New York, Outdoor Workers, 1 Ozone Season							
	0.01	0.13	0.01	0.1	0.3	0.01	0.75	0.01
	0.04	0.5	0.05	0.5	0.35	0.13	0.8	0.1
	0.06	0.83	0.1	0.75	0.4	0.22	0.85	0.3
	0.1	0.999	0.2	0.95	0.5	0.45	0.92	0.5
			0.25	0.99	0.57	0.5	0.99	0.9
					0.7	0.62		
					0.75	0.99		
BIBW10:	Expert B, Mild Lesions, Los Angeles and New York, Outdoor Workers, 10 Ozone Seasons							
	0.01	0.13	0.01	0.1	0.5	0.01	0.8	0.01
	0.04	0.5	0.05	0.5	0.53	0.13	0.84	0.1
	0.06	0.83	0.1	0.75	0.56	0.22	0.89	0.3
	0.1	0.999	0.2	0.95	0.61	0.45	0.95	0.5
			0.25	0.99	0.65	0.5	0.99	0.8
					0.76	0.62		
					0.8	0.99		
BOBC1:	Expert B, Moderate Lesions, Los Angeles and New York, Children, 1 Ozone Season							
					0.105	0.01	0.2	0.01
					0.13	0.13	0.24	0.1
					0.16	0.22	0.32	0.3
					0.21	0.45	0.43	0.5
					0.25	0.5	0.62	0.75
					0.35	0.88	0.74	0.95
					0.4	0.99	0.8	0.99
BOBC10:	Expert B, Moderate Lesions, Los Angeles and New York, Children, 10 Ozone Seasons							
			0.01	0.01	0.3	0.01	0.4	0.01
			0.02	0.1	0.34	0.13	0.5	0.1
			0.07	0.5	0.37	0.22	0.63	0.3
			0.15	0.95	0.43	0.45	0.79	0.5
			0.2	0.99	0.48	0.5	0.87	0.8
					0.54	0.84	0.9	0.99
					0.6	0.99		

TABLE C.1 (Cont'd)

Response Rate and Cumulative Probability, by Ozone Concentration								
Code	0.025 ppm		0.050 ppm		0.075 ppm		0.100 ppm	
	R	F	R	F	R	F	R	F
BOBW1:	Expert B, Moderate Lesions, Los Angeles and New York Outdoor Workers, 1 Ozone Season							
					0.005	0.01	0.02	0.01
					0.03	0.13	0.09	0.1
					0.06	0.22	0.16	0.3
					0.11	0.45	0.25	0.5
					0.15	0.5	0.4	0.75
					0.25	0.88	0.5	0.95
					0.3	0.99	0.55	0.99
BOBW10:	Expert B, Moderate Lesions, Los Angeles and New York, Outdoor Workers, 10 Ozone Seasons							
					0.05	0.01	0.15	0.01
					0.08	0.13	0.24	0.1
					0.11	0.22	0.36	0.3
					0.16	0.45	0.5	0.5
					0.2	0.5	0.57	0.8
					0.25	0.84	0.6	0.99
					0.3	0.99		
CIBB1:	Expert C, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, 1 Ozone Season							
	0	0	0.1	0.01	0.17	0.05	0.25	0.01
	0.03	0.28	0.2	0.3	0.35	0.5	0.4	0.3
	0.05	0.5	0.25	0.5	0.5	0.85	0.5	0.5
	0.07	0.79	0.35	0.85	0.75	0.99	0.7	0.85
	0.1	0.99	0.3	0.99			1	1
CIBB10:	Expert C, Mild Lesions, Los Angeles and New York, Children and Outdoor Workers, 10 Ozone Seasons							
	0.01	0.01	0.2	0.01	0.42	0.01	0.6	0.02
	0.09	0.25	0.4	0.25	0.65	0.25	0.86	0.25
	0.15	0.5	0.5	0.5	0.75	0.5	0.95	0.5
	0.24	0.75	0.62	0.75	0.83	0.75	0.98	0.75
	0.4	0.99	0.8	0.99	0.99	0.99	0.999	0.999

TABLE C.1 (Cont'd)

Response Rate and Cumulative Probability, by Ozone Concentration								
Code	0.025 ppm		0.050 ppm		0.075 ppm		0.100 ppm	
	R	F	R	F	R	F	R	F
COBB10:	Expert C, Moderate Lesions, Los Angeles and New York, Children and Outdoor Workers, 10 Ozone Seasons							
	0.001	0.001	0.02	0.05	0.045	0.05	0.22	0.05
	0.05	0.5	0.05	0.25	0.14	0.25	0.4	0.25
	0.1	0.75	0.12	0.5	0.25	0.5	0.5	0.5
	0.25	0.95	0.25	0.75	0.41	0.75	0.65	0.75
			0.43	0.95	0.64	0.95	0.93	0.95
DILB1:	Expert D, Mild Lesions, Los Angeles, Children and Outdoor Workers, 1 Ozone Season							
			0.15	0.01	0.45	0.01	0.64	0.01
			0.3	0.3	0.49	0.35	0.77	0.3
			0.4	0.5	0.58	0.5	0.85	0.5
			0.5	0.75	0.67	0.6	0.89	0.62
			0.6	0.99	0.76	0.99	0.99	0.99
DILC10:	Expert D, Mild Lesions, Los Angeles, Children, 10 Ozone Seasons							
			0.3	0.01	0.65	0.01	0.84	0.01
			0.42	0.3	0.68	0.19	0.9	0.3
			0.48	0.5	0.76	0.5	0.92	0.5
			0.59	0.75	0.84	0.6	0.95	0.62
			0.7	0.99	0.91	0.99	0.99	0.99
DILW1010:	Expert D, Mild Lesions, Los Angeles, Outdoor Workers 10 Ozone Seasons							
			0.3	0.01	0.55	0.01	0.75	0.01
			0.42	0.3	0.59	0.25	0.83	0.3
			0.48	0.5	0.68	0.5	0.87	0.5
			0.59	0.75	0.77	0.7	0.9	0.62
			0.7	0.99	0.85	0.99	1	1
DINB1:	Expert D, Mild Lesions, New York Children and Outdoor Workers, 1 Ozone Season							
			0.25	0.01	0.4	0.01	0.7	0.01
			0.4	0.25	0.6	0.3	0.75	0.05
			0.5	0.5	0.7	0.5	0.85	0.5
			0.67	0.8	0.8	0.9	0.9	0.9
			0.75	0.99	0.88	0.99	0.999	0.99

TABLE C.1 (Cont'd)

Response Rate and Cumulative Probability, by Ozone Concentration								
Code	0.025 ppm		0.050 ppm		0.075 ppm		0.100 ppm	
	R	F	R	F	R	F	R	F
DINB10:	Expert D, Mild Lesions, New York, Children and Outdoor Workers, 10 Ozone Seasons							
			0.4	0.01	0.6	0.01	0.8	0.01
			0.53	0.25	0.77	0.3	0.9	0.15
			0.7	0.5	0.82	0.5	0.95	0.5
			0.78	0.8	0.91	0.9	0.97	0.9
			0.82	0.99	0.99	0.99	1	1
DOLB1:	Expert D, Moderate Lesions, Los Angeles, Children and Outdoor Workers, 1 Ozone Season							
			0.02	0.01	0.08	0.01	0.18	0.01
			0.1	0.25	0.245	0.6	0.23	0.3
			0.15	0.5	0.35	0.8	0.31	0.5
			0.25	0.99	0.47	0.99	0.43	0.75
							0.63	0.99
DOLC10:	Expert D, Moderate Lesions, Los Angeles, Children, 10 Ozone Seasons							
			0.02	0.01	0.155	0.01	0.3	0.01
			0.1	0.25	0.3	0.5	0.37	0.3
			0.15	0.5	0.5	0.85	0.47	0.5
			0.25	0.99	0.6	0.99	0.61	0.75
							0.8	0.99
DOLW10:	Expert D, Moderate Lesions, Los Angeles, Outdoor Workers, 10 Ozone Seasons							
			0.02	0.01	0.135	0.01	0.27	0.01
			0.1	0.25	0.285	0.6	0.31	0.3
			0.15	0.5	0.4	0.85	0.38	0.5
			0.25	0.99	0.5	0.97	0.49	0.75
							0.68	0.99
DONB1:	Expert D, Moderate Lesions, New York, Children and Outdoor Workers, 1 Ozone Season							
			0.01	0.01	0.02	0.01	0.01	0.01
			0.05	0.5	0.05	0.25	0.2	0.25
			0.1	0.9	0.15	0.5	0.25	0.3
			0.2	0.99	0.2	0.67	0.33	0.5
					0.25	0.75	0.4	0.75
					0.35	0.95	0.5	0.95
					0.4	0.99	0.67	0.99

TABLE C.1 (Cont'd)

[illegible]

TABLE C.1 (Cont'd)

Response Rate and Cumulative Probability, by Ozone Concentration								
Code	0.025 ppm		0.050 ppm		0.075 ppm		0.100 ppm	
	R	F	R	F	R	F	R	F
EONB1:	Expert E, Moderate Lesions, New York, Children and Outdoor Workers, 1 Ozone Season							
					0	0	0	0
					0.1	0.5	0.1	0.36
					0.2	0.82	0.2	0.5
					0.33	0.99	0.5	0.99
EONB10:	Expert E, Moderate Lesions, New York, Children and Outdoor Workers, 10 Ozone Seasons							
					0.05	0.01	0.1	0.01
					0.15	0.5	0.25	0.5
					0.33	0.99	0.5	0.99
FIBB1:	Expert F, Mild Lesions, Los Angeles and New York Children and Outdoor Workers, 1 Ozone Season							
	0.5	0.01	0.96	0.01	0.97	0.01	0.99	0.001
	0.8	0.2	0.98	0.5031	0.99	0.9	0.999	0.999
	0.9	0.975	1	1	0.996	1		
FIBB10:	Expert F, Mild Lesions, Los Angeles and New York, Children, and Outdoor Workers, 10 Ozone Seasons							
	0.5	0.01	0.96	0.01	0.97	0.01	0.99	0.001
	0.8	0.2	0.98	0.5031	0.99	0.9	0.999	0.999
FOBB1:	Expert F, Moderate Lesions, Los Angeles and New York, Children and Outdoor Workers, 1 Ozone Season							
	0.001	0.01	0.07	0.01	0.07	0.01	0.99	0.001
	0.01	0.5	0.22	0.05	0.22	0.02	0.999	0.999
	0.05	0.99	0.37	0.12	0.47	0.1		
			0.57	0.5	0.67	0.5		
			0.67	0.89	0.77	0.97		
			0.77	0.99	0.87	0.99		

TABLE C.1 (Cont'd)

Response Rate and Cumulative Probability, by Ozone Concentration								
Code	0.025 ppm		0.050 ppm		0.075 ppm		0.100 ppm	
	R	F	R	F	R	F	R	F
FOBB10:	Expert F, Moderate Lesions, Los Angeles and New York, Children and Outdoor Workers, 10 Ozone Seasons							
	0.001	0.01	0.1	0.01	0.1	0.01	0.99	0.001
	0.01	0.5	0.25	0.05	0.25	0.02	0.999	0.999
	0.05	0.99	0.4	0.12	0.5	0.1		
			0.6	0.5	0.7	0.5		
			0.7	0.89	0.8	0.97		
			0.8	0.99	0.9	0.99		

^aR denotes response rate (fraction of the population having either mild or moderate lesions).

^bF denotes cumulative probability.

APPENDIX D
QUALITATIVE JUDGMENTS

APPENDIX D

QUALITATIVE JUDGMENTS

Qualitative judgments were obtained from the experts during the first round of encodings and the workshop. In the former instance, the risk assessment team and each expert engaged in extensive discussion, guided by the protocol (Appendix A), before encoding the quantitative judgments. The notes taken by team members were subsequently arranged topically and are paraphrased in Section D.1. During the workshop, the discussion among the experts was free ranging but proceeded according to a fixed agenda and was facilitated by EPA staff and the risk assessment team. In Section D.2, the agenda topics are listed and the discussions are summarized. The summary relies primarily on notes taken by Dr. James Raub; however, those notes were supplemented by those taken by Dr. David McKee and members of the risk assessment team.

The statements are labeled by the code letters assigned to the experts. The only exception was when such labeling might reveal the expert's identity. In those cases, the statement is attributed to Expert X.

D.1 DISCUSSIONS PRECEDING THE FIRST ROUND OF ENCODING

D.1.1 Extrapolation from Animals to Humans

Expert A. The exposure regime for the EPA chronic study is too peaked. In light of the California data, the peak-to-mean ratio should be less.

No animal studied has failed to show centriacinar lesions, including mice, rabbits, dogs, two species of monkeys, guinea pigs, hamsters, and several strains of rats. The effects may be different in time and intensity, but they are always present. Humans almost certainly get centriacinar lesions as well.

Concerning epidemiology research, the Seventh-Day Adventist study (Euler et al., 1988) is as useful as the Detels et al. (1981) study.

Expert B. The literature on primates is more useful than that on rats for extrapolating to humans. This is because of (1) similarities in structure and cell population; (2) species-specific antioxidant mechanisms (e.g., glutathione and its precursors are depleted by ozone; because primates have less reserve, they require a steady-state to import these substances); and (3) cell types at the centriacinar site (i.e., different cell types have different glutathione levels). Intraspecies extrapolation studies have not yet been done.

Epidemiological studies are characterized by so much noise and multicollinearity that it is hard to pick out the ozone effect.

I have a bias against biochemical studies because they are "whole-lung" analyses; the target site is only about 5% of the lung.

The field is just coming to the point where definitive work can be done.

Expert C. The low dose work is most useful. Certain of the work on monkeys is O.K. The Lippmann et al. (1983) field study is very powerful; it is the only one with good control on dose, activity, etc. Although six epidemiological studies are flawed, they show the same effect. More studies like Lippmann's are needed. Together they may lead to good answers for ozone. We are approximately five years away from good predictive models, which must then be validated in field or epidemiological studies.

More species-specific and human data are needed.

Expert D. High levels of ozone (>0.2 ppm in humans) interfere with an enzyme (lysyl oxydase) needed for proper repair; therefore, an acute phenomenon leads to chronic effects. With some probability, the result is lesions; with the remaining probability, the result is emphysema. The animal data suggest that the probability of emphysema approaches zero, while the human data suggest that the probability is distinctly greater than zero.

At high exposures, the type of exposure pattern clearly affects the resulting damage. There may or may not be an adaptive process for constant (24-hour) exposure.

Expert E. The most useful studies have been those involving chronic exposures and multiple endpoints. Studies involving acute exposures are not helpful. The studies by EPA, University of California, Davis, and General Motors are useful. The next step is to vary exposure patterns.

The epidemiological studies are not much help. More useful would be a prospective, long-term, high-cost study.

The results across species are likely to be "about the same" at cellular and subcellular levels. Animals are giving us the right leads. They have told us what endpoints to look for and the exposure levels of concern.

Expert F. The Detels et al. (1981) study has been said to have shortcomings, but it is important. It suggests a two to three times greater loss of lung function in Los Angeles populations compared with other cities.

Confounding factors with regard to ozone effects include smoking, nutritional status, and other disease-producing agents. Together, they all play a role in causing effects.

The answer to those who ask why we do not see more emphysema in Los Angeles if the air quality is so bad is: nobody is looking for it.

D.1.2 Dosimetry

Expert A. Dosimetry modeling is a good idea. The basic model is very solid and has considered the right things. However, the results are not startling, and there are very few data to back them up. Basic data are still missing to adjust the parameters, particularly as they relate to changes in ventilation. Comparisons are among exercising humans, at-rest humans, and at-rest rats and monkeys, but not exercising rats or monkeys.

Dosimetry graphs 4 and 5 indicate that children may have more intense lesions. That is, for a fixed exposure, one can expect a child to receive a greater dose than an adult. However, the Overton et al. (1990) paper, which is the basis for the model of delivery to sensitive tissues in children, has too few data points on children. This weak basis increases the uncertainty in making inferences regarding children.

Expert B. I disagree with the generation/airway definitions used in the dosimetry modeling. Rats have a 10-generation difference from humans in the target site, and there is still some injury. The results do not mean much of anything. The predictive dose patterns for humans match the monkey patterns, but monkeys show a greater impact than rats. If the dosimetry model is correct, then primates have more sensitive tissue.

Expert C. The conclusion that a rat receives a larger dose than a child is not scientifically supportable. Rats have very efficient noses, whereas the model argues that human noses remove more ozone than rat noses.

The assumption regarding recovery rate is too low. I disagree with the contention that nose breathing is equivalent to mouth breathing.

The Weibel model (Weibel, 1963) is not appropriate; path length and distal volume are key parameters. Was the experiment done correctly?

Expert E. I am wary of the model results. There seems to be much uncertainty concerning rats versus humans.

D.1.3 Definition of Health Endpoint

Expert A. The focus on centriacinar lesions is correct, and I can live with the definitions of mild versus moderate lesions. Although the definitions are not perfect, they are as good one can come up with.

Expert B. The focus on centriacinar lesions is correct. Normally, one does not think of lesions as mild or moderate, but this distinction is satisfactory for these purposes. The distinction may lie more in the skill of the researcher in picking out the lesion; if one is

sufficiently skilled, one can probably find a lesion with a light microscope. The definition is good if standard microscopy technique is used.

The definition I used was that a mild lesion cannot be distinguished with routine histopathology techniques (e.g., paraffin), whereas a moderate one can be.

Expert E. The definitions of mild and moderate lesions are clear, but are limited to morphological lesions. No one has been able to put structure and function together to specify health consequences.

Expert F. It is correct to be concerned about centriacinar lesions. However, it would have been preferable to define mild lesions in broader terms, that is, from data that can be reasonably anticipated with new advances in technology or from actual data derived from a variety of highly sensitive methodologies. Mild could be consistent with severe, but highly localized, damage or minor, but widespread, alteration. For a full definition, it is necessary to specify both extent and severity. Further, the structural damage observed may not reflect the magnitude of functional alteration. For my encodings, I used "mild" to mean subtle and "moderate" to mean overt.

D.1.4 Time Scale, Sequence of Effects, and Effect of Time Variation

Expert A. Centriacinar lesions form more rapidly than people think. The time scale is weeks, not months. Lesions have been seen in animals in six to eight weeks, and there is no reason to think matters are different in humans.

The eight-hour average is good; so is a four- or six-hour average.

It is worse to have a respite than not to. A whole new generation of sensitive cells develops during respite. Resolution is worse than no resolution because adaptation stops. The result is a new generation of sensitive cells that then exhibits a greater response.

After a one-day exposure, lungs are back to "as normal as they will ever be" after 21 days.

Inflammation leads to changes in the epithelium, which leads to remodeling. The inflammation and epithelium lesions occur in a matter of hours; remodeling takes six to eight weeks. The intensity of the lesion depends on the peaks of the exposure, whereas the existence of the lesion depends on the average exposure.

The number of hours per day to induce an effect is not important. The threshold may be somewhere between 2 and 6 hours; however, there is not much difference in the effect between 6 and 10 hours of exposure.

With regard to the number of days per week, some studies have shown five days to be worse than seven days.

We do not know enough to discriminate between the effects of different exposure patterns. The subtleties of exposure patterns may be important, but all that is still a matter of conjecture.

It is hard to relate the EPA encoding protocol to other studies. The daily pattern is not crucial. EPA's exposure profile just increased the error. Intermittent, multiple-day periods of polluted air and clean air are important protocol design considerations.

Concentration is the most important factor, not time. The concept of concentration multiplied by time is wrong.

Expert B. During the first 24 hours, cellular necrosis and acute inflammatory response, both of which are cellular injuries, occur. The question remains as to whether this happens only once, even if the exposure continues. There is a 24-hour cycle for injury, but some question about whether the replacement cells are adapted. One never sees acute inflammatory response after the first time, but the cell population is different. During the first three to five days, there is no difference between continuous and intermittent exposure. By seven days, the cell population starts to differ and fibroblasts start to produce collagen. Beyond three months, the effects are irreversible.

The effects of continuous versus intermittent exposure differ only in degree, not in pattern.

After only a single exposure, one is back to normal after one week. Chronic problems start after exposure every second day for a week. Effects of exposure over three months are irreversible. Once cells change, they do not change back for a long time (i.e., for at least one year, according to data) because lung cells turn over very slowly.

Expert C. Cumulative ozone dose at low levels (<0.3 ppm) causes damage by reacting with tissue, which results in edema and cell injury. The peaks in exposure do not really matter; however, they are important at higher (acute) levels. One can expect a progressive (linear) increase in effect as a function of dose, but that effect tails off after a while.

Epithelial injury is reversible. Interstitial effects are more serious. Stiffening (aging) of the lungs results from chronic exposure to ozone.

With regard to the role of respites, one can argue both ways.

Expert D. Acute effects occur quickly in both rats and humans, but it takes approximately four to six months for chronic effects to develop in rats.

Respites may be important. The theory is that damage and misrepair over time are very important.

Expert E. It is better to think about peak rather than cumulative exposure. At very high peak concentrations, repair mechanisms could be overwhelmed, and irreversible damage could

result. This could be true, regardless of duration of exposure. However, lower concentrations (<0.25 ppm) appear to cause only mild changes that are largely reversible, again regardless of duration.

Expert F. Peaks are very important, and overall seasonal means or averages are less so. The Los Angeles pattern seems more "pathologic" than the New York one, presumably because of differences in pattern.

D.1.5 Degree of Repair

Expert A. Too few studies have been done. Everyone agrees that repair occurs, but how complete is the repair? When the exposure ceases, the damage mechanisms set in motion will continue to operate even while repair mechanisms are operative. A person is worse off after 10 ozone seasons than after one.

Some data demonstrate that collagen continues to form after exposure ceases. Once the collagen is laid down, it is there for a long time. It may go away, but not for a long period.

Expert B. Epithelial hyperplasia is seen after three months of exposure, and it is not reversed six to nine months later. After three to four months (and sometimes up to nine months) at low ambient levels, fibrosis is worse and epithelial changes are not reversed. The only thing that improves is the inflammation. Collagen deposition continues after exposure ceases.

Expert C. Repair will take place, but it may be faulty.

Expert D. Type II cells are better able to resist oxidants than are other cell types.

Expert E. A naive (i.e., previously unexposed) lung exposed to a higher level of ozone will experience some inflammation, permeability changes, cell turnover, changes in lymph nodes, etc. However, if the exposure stops or levels off, these changes will subside.

A lot happens in the first three to four days of exposure, but the response subsides after about one week. This conclusion is shown by the studies conducted by EPA, General Motors, and University of California, Davis.

A lesion can be repaired, but the degree of repair depends on the exposure concentration. If the concentration is high enough, there will be residual damage due to repair mechanisms being overwhelmed.

If the exposure is "low enough," each ozone season begins with the lungs in the same condition as at the beginning of the last period. That is, mild changes are likely to be reversible.

Expert F. There is little reason to believe in adaptation for this phenomenon.

D.1.6 Interaction with Other Pollutants

Expert A. We know so little, it is difficult to say anything.

Expert B. All pollutants have an impact. Sulfur dioxide, nitrogen dioxide, and ozone are often thought of as having different sites, but it does not appear to be so. Data suggest that there is no synergy for sulfur dioxide and ozone. The effects of different pollutants may be additive.

Expert C. There is some (a small amount of) synergism between pollutants, but most of the injury is caused by ozone. Ozone is less prevalent than other pollutants, but it is the "big bullet," whereas the others are "small." If ozone alters clearance, then other particles can become a problem.

Expert D. Ozone is the most important pollutant, but others are clearly involved.

At low levels sulfur oxides and ozone are more than additive; however, at high levels there is not much interaction.

The difference between New York and Los Angeles is smaller now than it was 20-30 years ago.

Expert E. There is no convincing evidence to suggest synergism between ozone and other pollutants.

Expert F. There are synergies between ozone and other pollutants; the mix of pollution is additive.

We must be concerned about other oxidants, like peroxyacetyl nitrate, that are more reactive than ozone. This oxidant is 40% stronger than ozone. Since it and other highly reactive oxidants are not measured, an ozone reading may understate oxidants by as much as 40%, according to studies in the California South Coast Air Basin (Tuazon, Winer, and Pitts, 1981; Grosjean, 1983).

D.1.7 Stratification

Note: All six of the experts stratified on 1 versus 10 seasons, although Expert E did so only for moderate lesions.

Expert A. The monthly profiles of Los Angeles and New York, which are more similar than expected, are close enough together to give rise to similar health effects. Even though the "respite" time is a couple of months shorter in Los Angeles, it does not matter because the off-season values, on average, look similar. But, after discussing the air quality exposure data, lesions might be of greater intensity in Los Angeles than in New York. The air quality patterns do not warrant breaking the two areas out.

The population groups are not sufficiently different to warrant breaking them out separately. The consequences might be greater in children; they would have a greater intensity of lesions. Maybe their lesions would be "moderate" when those of the adults would be "mild." This conjecture is supported by the Davis studies of adult versus child. The dosimetry is somewhat different for kids.

If a controlled experiment were done, smoking should be a design factor, not just randomized. For this encoding, however, it can be assumed that smokers are randomized throughout the population. It is therefore possible to ignore them as a separate group. The same is true for chronic obstructive pulmonary disease and nutritional status.

Expert B. It is not necessary to distinguish between New York and Los Angeles. Things would probably be worse after 10 seasons than 1 season.

Children aged 6 to 13 are going through a rapid growth phase and probably have a higher level of sensitivity to fibrotic changes. Because kids are more resistant to some things, adults may be more sensitive to some kinds of injury. Thus, stratify on children versus adults.

It is O.K. to fold smokers in as part of a general population. However, they are at much greater risk than the rest of the population because they are already so compromised that additional stress is bound to make things worse.

Expert D. It is not possible to say whether children are more or less susceptible than adults.

Expert F. Los Angeles and New York should be considered separately because of differences in the patterns of exposure. The very high peak values in Los Angeles (second-stage alerts) are important.

D.1.8 Health Significance of Effects

Expert A. The effects are similar to cigarette-induced lesions, but less severe. The only difference is the pigmented macrophage with smoking.

The lesion is important, but it is not directly linked to functional impairment. The lesion involves inflammation, changes in epithelial thickness, remodeling of airways, and changes in airflow patterns. Changes in the epithelial thickness do not change diffusion capacity because such changes only occur in a very small portion of the lung.

The ciliated cell in the airway is the most damaged. Type I cells are replaced by Type II cells. In the centriacinar region of the lung, some Type I cells will be replaced by bronchiolar cells. Consequently, there will be one less generation of alveolar ducts and one more of bronchiolar ducts. This shift is important because it changes the ventilation pattern to the acinus. It may also change the pattern of deposition and increase particle deposition. There is probably increased susceptibility to infection because the clearance mechanism is reduced in effectiveness.

Emphysema is not an endpoint of concern with ozone.

(Note: At this time, a diagram based on work by Utell [1989] and Spizer and Tager [1979] on loss of lung function with age and the acceleration of the process by ozone exposure was presented. Three of the experts explicitly endorsed the figure as it related to ozone exposure.)

Expert B. I agree with the figure showing depletion of lung function reserves with age due to ozone exposure. (This figure, adapted by a member of the risk team from Utell [1989], shows [in a generic fashion] a decrease in lung function with age, with some threshold level indicated as the point below which the loss of function is deleterious and another level below which death occurs. Ozone is shown as hastening the rate of lung function decline.)

Ozone exposure increases susceptibility to infection.

Expert C. Ozone affects the ability to clear asbestos from the lung. It may be considered to be a "defense suppressor" or to enhance the retention of other carcinogens.

Chronic exposure causes stiffening (aging) of the lungs. If ozone causes epithelial injury and fibrosis, then those conditions would reduce the reserve capacity of the lung. An olympic athlete would notice such effects from chronic exposure, but a couch potato would not.

Other pulmonary diseases become more serious in the presence of ozone-induced injury to the lung. Quality of life, rather than length of life, is the dominant effect. Life may not be threatened, but activity capacity will be affected. Ozone alone is probably O.K., but ozone plus other injury has the potential to cause trouble.

Expert D. Quality of life is restricted, and there are debilitating effects; however, it cannot be said whether longevity is affected.

Expert E. It does not appear that formation of lesions leads to emphysema or cancer. Possibly the lesions lead to fibrosis. Quality of life (independent of lesions) could be affected if enough of the lung were involved, but aging effects seem to swamp the effects of lesions in the centriacinar region of the lung.

One does not know if there is increased probability of developing other diseases (infections). One should not charge a larger life insurance premium for a person in Los Angeles

versus Iowa. There would be a difference if the insurance covered acute effects like coughing, wheezing, etc.

Expert F. The best correlate for functional decrement is emphysema. Stiffening of the lung also contributes to the decrement. Some thickening occurs from edema, which would reverse without additional exposure.

Ozone exposure leads to more macrophages. Changes due to ozone do not appear to be fully reversible.

One should be concerned about air pollution increasing cancer metastasis, but the magnitude of the effect is unknown.

I would be very surprised if centriacinar lesions do not produce centrilobular emphysema. They certainly produce chronic bronchiolitis (small airway disease). Chronic bronchiolitis is the most underdiagnosed disease.

The Utell figure (described above) showing ozone depleting lung reserves with age is correct.

One should be concerned about the relationship between ozone and immunosuppression. Is there a relationship to autoimmune deficiency syndrome (AIDS)?

Expert X. One should be very concerned about centriacinar lesions. The most important question is whether there is an inordinate depletion of reserve in the lung.

Centriacinar lesions can be caused by many things (e.g., ozone, nitrogen dioxide, viruses, and pesticides). The centriacinar region of the lung is "very vulnerable," very delicate.

No one agent is responsible for disease. Disease is the interactive effect of many things, the total complex.

Emphysematous disease may very well be one of the endpoints of centriacinar damage. Even in its early stages, centriacinar damage may have great functional significance because a lesion that involves only 15% of the lung parenchyma, but is entirely restricted to the centriacinar region, alters essentially 100% of the airflow to all alveoli. Emphysema symptoms may not become evident until 75% of lung structure and/or function has been lost. The differential diagnosis of chronic bronchitis and emphysema is presently very poor science.

D.1.9 Populations at Risk

Expert A. Smokers as a group may be at increased risk; however, smokers get so many centriacinar lesions from smoking that ozone exposure results in just a small additive effect.

There are problems with the term "responders." The presence of sensitive airways may not correlate with the presence of lesions. Physiological response is based on airway response. Morphological response is separate.

Expert B. Very young children are more resistant to ozone exposure. So, adults may be more sensitive in this case. But children 6 to 13 years old have very high sensitivity.

It is not necessary to distinguish smokers from nonsmokers.

Diet makes a big difference at low exposure levels, particularly vitamin E. One could predict who would get lesions at low-level exposures by looking at vitamin E and glutathione levels in blood.

Expert F. Since children tend to be less concerned than adults about vigorous exercise during smog periods, and since the lungs of children are in a developmental stage, air pollution may have a relatively greater adverse effect on their lung reserves than on those of mature adults. The rate of decline in lung function, once adulthood is reached, may be greater for children who have resided in areas that frequently exceed air quality standards. These children may have comparatively less lung reserve at the time they reach adulthood.

D.1.10 Research Needs

Expert A. Lesions are not uniform. We need to go after a global view of the lung. Variation among lesions is important. The data do not account for differences in intensity. We need to sample more extensively to see variation in lesions, but the emphasis on sophistication leads to sampling a very small area with electron microscopy.

Simple exposure patterns should be used because the pattern does not matter and only adds to the chance of error.

Extrapolation of data from animals exposed at rest to possible effects on humans exposed while exercising is a major problem.

Expert B. The most useful research is to determine how similar the human lung is to the lungs of other primates and to study those primates.

Expert C. While each of the several individual epidemiological studies conducted has flaws, they all show similar effects. We need more field studies like Lippmann et al. (1983). Together, they may lead to good answers for ozone. We are approximately five years away from good predictive models for extrapolating animal data to humans. These models must be validated by field and epidemiological studies.

We need more species-specific and human data.

D.2 DISCUSSIONS DURING THE WORKSHOP

The workshop took place in Durham, North Carolina, on September 16, 1989. Attended by the six experts, EPA staff, and the risk assessment team, the workshop was chaired by Dr. Judy Graham of EPA. Although she led the discussion, the experts were the main participants. By design, the other attendees participated in only a very secondary fashion.

The objectives of the workshop were to allow the experts to exchange viewpoints and perspectives and to provide a record of their comments. Discussion was to focus primarily on potential chronic health effects in humans exposed to ambient levels of ozone. It was emphasized for all participants that consensus was neither expected nor required and that the discussion was not relevant to the current round of NAAQS development.

The workshop agenda listed the topics for discussion in the following order: (1) health significance and nature of effects; (2) definition of exposure scenarios; (3) dosimetry modeling; (4) sequence of response, including time scale of effects, effects of time-varying concentrations, and degree and role of repair; and (5) interaction with other pollutants. There followed a discussion of the discriminatory variables for encoding, a presentation and discussion of the results of the first round encodings (with individuals labeled by code letters and knowing only their own code), and a discussion of research needs. Only the comments of the six experts on substantive issues and research needs are summarized below. Comments by the moderator to introduce topics and help refocus the discussion are indicated by "Graham."

D.2.1 Definition of Health Endpoint

Graham. Were the definitions of the health endpoints well taken?

Expert F. We need to explore the long-term consequences of centriacinar lesions, not just obstruction. An inventory of structures, or of centriacinar lesions, is needed.

Expert E. The endpoint chosen (centriacinar lesions) is appropriate for ozone exposure. A leading question, however, is whether mild ozone-induced lesions are detectable in humans in light of their total exposure to other environmental pollutants. Bronchoalveolar lavage in humans shows that latent respiratory disease exists in the population at large.

Expert F. Walking pneumonia is common in the "well-population," especially from mycoplasma and viruses. The "usual" pneumonias also differ. For example, pneumococcus is intraluminal disease with, on average, less destructive effect than staphylococcal broncopneumonia.

D.2.2 Health Significance

Graham. What about mild versus moderate lesions?

Expert C. It is hard to determine significance based on pathology alone. Rather, pathology must be combined with pulmonary function. A study by Pinkerton et al. (1989) shows the importance of ozone exposure on fiber clearance. The ozone lesions were "mild" but affected asbestos clearance through damage to the epithelial cells, cilia, or phagocytic cells. Therefore, coexposure of ozone and particles is important. One might speculate that asbestos deposits in the centriacinar region of the lung where the ozone effect occurs.

Expert X. The picture is not simple; it is necessary to consider combined exposure in humans. Asbestos, viruses, and ozone all cause centriacinar lesions. Is there synergism? Another area of concern is cancer. More metastasis occurs with exposure to ozone and nitrogen dioxide. It would be prudent for cancer patients to stay in clean air (based on Richters's [1988] work and work by the Japanese).

Expert D. Richters's work (1988) used metastatic cells, not primary lung cells. The mechanism is unknown, but the endothelium may be affected by nitrogen dioxide.

Expert B. Homeostasis is affected by ozone exposure. The target population is similar for ozone and carcinogens. Bioactivity increases with ozone exposures near ambient levels in combination with nitrosamines. Witschi (1988), using nitrosamines, found that small-cell lung tumors were generated in 80% of ozone-exposed animals. Therefore, there is potential for a baseline change to affect other diseases.

Expert X. Richters's work (1988) on ozone involved an immune response. Thus, there is potential interaction of ozone in individuals with immunosuppression (e.g., AIDS).

Graham. Going back to generic questions of chronic risk, what do centriacinar region figures and effects mean?

Expert A. Many pollutants cause lesions in the centriacinar region; it is an important region in the lung. All species exposed to ozone show centriacinar lesions.

Expert C. I believe in general that there is a dose-response curve, although we may disagree on its shape and the impact of other pollutants. Coexposure may make things much worse. The centriacinar region is the region with the highest dose, and it should therefore be of greatest concern. Other regions may be protected. The centriacinar region is the marker for the other regions. Changes in clearance, homeostasis, and function are important. It is hard to determine what is most serious and to quantify what are mild, moderate, or severe lesions.

Graham. What are the implications of mild lesions when only ozone is seen, as in a chamber?

Expert E. The mild centriacinar lesion in humans is not a serious concern. Ozone exposure alone will not affect quality of life, but it may reset homeostasis for other potential exposures or aging. I am more concerned about the mix of pollutants than about ozone alone.

Expert X. I have seen 15- to 25-year-old individuals (violent death cases) who were apparently healthy and yet had severe centriacinar disease. Most young adults show some centriacinar lesions, and the majority of these in my experience have from slight to moderate centriacinar alteration, often with other lesions, such as chronic bronchitis.

Expert C. The rat underestimates ozone exposure. Ozone is more strongly detected in the nonhuman primate.

Expert A. The centriacinar region of the lung is important functionally. It may cause ventilation and perfusion differences in the lung.

Expert C. You are asking whether ozone alone is a problem. The real question should be: what happens in combination with all other pollutants? We should be worried about significant decrements in lung function later in life.

Graham. Is part of the problem that the ozone cannot be detected?

Expert B. Because of the reserve capacity of the lungs, lung physiology can only detect a 30-50% decrease in the cross-sectional area of the centriacinar region.

Expert D. Physiology cannot detect subtle changes in the lung; reserve capacity is too large. Ozone could set up a change in homeostasis (particularly in susceptible individuals) and cause concern over years of exposure. A person who can perform normally now may not be able to do so in 10 years because of living in an ozone nonattainment area.

Expert F. Fifty percent of the 40 million joggers are over the age of 35. Ten percent of these can be expected to test positive for evidence of coronary artery disease, with 25% of the 10% expected to show (by angiography) occlusion of one or more major vessels (i.e., roughly half a million).

D.2.3 Emphasis on Disease Etiology

Graham. Why aren't terms like fibrotic or emphysematic being used with ozone exposure?

Expert D. This issue concerns reversibility. Defining lung disease as fibrosis or emphysema is difficult.

Expert C. Ozone does not cause emphysema; it is more of a fibrotic disease. However, localized centriacinar fibrosis is not common in humans; the fibrosis is usually more diffuse. The effect of ozone exposure on gas flow (distribution) and clearance of particles is more important. Ozone does not have a good disease classification.

Graham. Should we spend billions of dollars to control ozone?

Expert F. Everybody loses lung function with age. Why? The loss of lung function with age is important.

Expert D. The rodent lung does not age like the human lung. Aging effects could be due to cumulative injury (e.g., loss of structural units -- interstitial tissue -- over time). In part, we may be losing function over time because of exposure to pollutants in cities.

Expert F. Loss of lung tissue does occur in humans over time. Emphysema is loss of lung tissue. The centriacinar lesions show loss of structural integrity of the lung and, therefore, loss of reserve capacity. What you are really asking is how long the lung of an ozone-exposed individual will last versus a person living in clean air.

Expert D. Centriacinar lesions in rats or in humans are fibrogenic and epithelial in nature. Since emphysema is more common in humans, what is the association with ozone exposure?

Expert C. Two diseases are probably going on.

Expert F. Peribronchiolar fibrosis is important in humans, including thickening of walls, inflammation, etc. However, this is a controversial area. How can we separate centriacinar emphysema with and without fibrosis?

Expert A. I liked the Utell (1989) diagram. Children are also important, however. Do we all start out with the same lung capacity? Certainly not. We need to consider ozone effects on lung development as well as on lung aging.

Expert F. It is necessary to look at subclinical effects (e.g., loss of reserve).

Graham. Now, the condition of quality of life is being raised. Should "death" be a marker on the Utell diagram, or should there be other markers such as "mortality"?

Expert C. Perhaps there should be several terms between "reserve" and "death." Ozone may affect the quality of life, but not mortality or morbidity directly. Compared with cigarette smoking, however, ozone exposure is a small problem (for public health regulations). If direct cancer effects are found in laboratory animals exposed to ozone, then mortality is a concern.

Expert X. Does cigarette smoking kill, or is it more appropriate to talk about facilitation of disease? Maybe we should ask what is the relative magnitude of smoking's adverse effect compared with other noxious agents?

Expert C. Yes, by heart and lung disease.

Expert F. Could there not be excess heart disease caused by ozone?

Expert C. Perhaps, but we have no evidence. We are talking about people who may have died sooner than otherwise.

Expert A. The quality of life is important. We (society) should be concerned with the reasons for early retirement.

Expert B. The economics of aging is important.

D.2.4 Definition of Exposure

A general discussion ensued that involved a member of the risk team and the experts regarding the exposure protocol for the encoding. Points covered included: (1) use of personal daily maximum eight-hour average concentrations for April through October; (2) Los Angeles versus New York as represented by 1983 data; (3) use of the Systems Applications, Inc., Personal Air Quality Model (PAQM) to account for indoor air, etc.; (4) the two cohorts of 6- to 18-year-old children and outdoor workers; (5) a single activity pattern per cohort; and (6) the assumption of open-window conditions for indoor air. No real disagreements with the assumptions emerged.

D.2.5 Dosimetry

Expert E. This is an important area in which we need more information. Much uncertainty exists.

Expert C. The definition of dosimetry is important. The information from models verifies that the centriacinar region receives the highest dose of ozone in all species, but we cannot use the model any further. We need to know how animal models will predict human exposure; the current data are controversial and confusing. For example, the model predicts that rats will receive larger doses than children, yet data exist showing that monkeys have higher dose-response relationships than rats.

Expert X. The monkey data will be presented at the Air and Waste Management Association's meeting next year. In conjunction with the nasal data presented by Harkema and his associates (Harkema, Hotchkiss, and Henderson, 1989; Harkema et al., 1987a, 1987b), we have looked at the centriacinar region in monkeys exposed to 0.15 ppm for 6 and 90 days, and to 0.30 ppm for 90 days. Monkeys show roughly two times the cell size changes and three times the epithelial cell damage as comparably exposed rats. Monkeys are therefore more sensitive than rats to ozone.

Expert D. I used the dosimetry information and was surprised that there was not much difference between children and workers. Rats get a greater dose to the target region, but little is known about comparative tissue sensitivity. For example, rats have decreased uric acid and increased antioxidants. The greater dose in rats was projected on the basis of nmol/surface area.

Expert C. There were many assumptions in the model predicting rat dose; only a small fraction of the $^{18}\text{O}_3$ was recovered. It is hard to believe data that have not been peer-reviewed.

Expert B. Rats are five times more efficient in clearing ozone. I also have concern about the dosimetry data.

Expert D. Gary Hatch (Hatch et al., 1989) tried to look at the surface area of the lung as a basis for the factor of two difference. Wiester's data (Wiester et al., 1988) extended that to a factor of 2.5.

Expert C. The amount cleared by the nose plays an important role. The rat nose clears more efficiently than the human nose. Oral versus nasal breathing must alter nasopharyngeal removal. Why does the model not show this?

Expert D. There are individual differences in removal. There are data that show it is the same. Forty percent is cleared in the human nose.

Expert E. Is the model sensitive to minute volume? [Answer – yes] Will it affect model predictions? [Answer – yes]

Expert F. What about the mucus effect? [Answer – most data are from bronchitis; they are probably not much different if mucus remains similar]

D.2.6 Sequence and Time Scale of Response

Expert B. The first three days of exposure constitute the important part of the response curve in the inflammation process.

Expert C. Is the effect at 12 months driven by peaks or by cumulative dose?

Expert B. If exposure is stopped, things begin to return to normal and eventually may get close to original conditions.

Expert C. Response curves are sensitive to concentration. Cumulative dose drives the response from three weeks to three months; peak concentration drives the acute response.

Expert X. I published data showing similar effects for intermittent (seasonal) and continuous exposure to ozone.

Expert C. This means background should be taken into account. Biochemical and cellular changes are produced rather than short-term tissue change.

Expert A. Dose rate is important. The threshold of this effect may be higher.

Expert C. Cumulative effects are important at low levels, as demonstrated in radiation biology.

Expert F. Direct effects of ozone may not be as important as the secondary effects from mediator cells.

Expert C. It is speculation, but more than likely a mild to moderate lesion is caused by the appearance of mediator cells.

From 3 to 12 weeks, a concentration-times-time effect may hold, but not for a longer time.

Expert X. Monkey exposure data (0.15 ppm and 0.30 ppm for 90 days) do not indicate a cumulative effect. Therefore, a concentration-times-time effect does not work.

Expert C. Ozone is radiomimetic; no threshold is apparent (theoretically).

Expert B. A threshold is apparent under certain conditions.

Expert C. Cellular transport or clearance could be affected all the way to zero.

Expert A. The threshold is not always detectable; concentration is more important than time.

Graham. Even when there is no ozone, damage may be continuing. Would we be better off to have high ozone in winter?

Expert D. Using protein as an inflammatory marker, concentration-times-time acute studies in rats exposed to 0.2-0.8 ppm for two to eight hours showed a polynomial relationship that is linear at high and low concentrations and curvilinear at middle concentrations.

With regard to adaptation, seasonal adaptation of rats to ozone exposure occurs; four months after exposure, the rats return to more sensitive conditions. Seasonal adaptation also occurs in humans exposed to smog. Also, cigarette smokers are less responsive to ozone.

Expert F. It must be determined whether a single exposure to ozone can cause a progressive effect. A smoldering insult may break out when an individual gets hit by an ozone peak. Homeostasis certainly changes with a single exposure.

D.2.7 Repair

Graham. Are the degree and role of repair important?

Expert X. There is irreversible disease in all people. What is important is the degree of reversibility of damage.

Expert A. The centriacinar lesion persists. Epithelial cell component changes are not always reversible. For example, bronchiolar cells cannot change back to alveolar cells. Once bronchiolarization (remodeling) takes place, it is not reversible.

Collagen deposition may or may not be reversible. The available data indicate that it is not, at least over the short recovery times that have been investigated.

Expert C. Destruction of alveoli and bronchiolarization do not revert back; some cell changes in the epithelium will revert back. It is too difficult to determine if loss of alveoli will be reversed.

Expert X. People at least 40 years old have definite lung loss. All adult lungs have emphysema; therefore, alveoli are lost permanently.

D.2.8 Interaction of Pollutants

Graham. Any further comment on the interaction of ozone with other pollutants?

Expert E. Ozone is one of the more important pollutants for centriacinar lesions, but it can be controlled. I am not convinced that synergism takes place; more research is needed.

Expert X. Normal, healthy individuals have three million asbestos fibers per gram of lung. Therefore, there is always the potential for peribronchial fibrosis and possible influence by ozone exposure.

Also, pathogens endogenous to the lung could be affected by immunosuppression. Ozone may be immunosuppressive.

At least one part of the centriacinar region would be affected in every individual. Data on 15- to 25-year-old human lungs indicate the following degree of centriacinar lesions: 25% show no effect, 25% show a minimum to slight effect, 25% show a slight to moderate one, and 25% show a moderate to marked effect.

Children may be more susceptible because of effects on the growing lung.

Expert A. Biochemical information indicates that very young animals may also be less susceptible.

Expert B. Data are not clear on the susceptibility of children. Research is needed. Remodeling of the lungs occurs during child development, and this logically suggests greater sensitivity.

Expert A. We cannot prove it, but the data we have suggest that children are more sensitive. Although the data are not yet in, we should use common sense, which says they are more sensitive.

Expert F. Drugs can also produce complicating effects.

Expert A. The rat lung has a terminal bronchiole alveolar duct centriacinar region, and the monkey lung has a terminal bronchiole/respiratory bronchiole/alveolar duct centriacinar region. The larger acinus of monkeys will receive more dose at the centriacinar region. This is why monkeys show more lesions than rats; primates are basically more susceptible because of the nature of their centriacinar regions. The rat retains 50% of the inhaled dose, whereas the monkey retains 70%.

D.2.9 Research Needs

B. Jordan (OAQPS). From the discussions held today, there is a reasonable probability that lesions occur in a certain segment of the population exposed to ambient air. How serious are the effects? Are changes in lung function indicators of more serious effects? Does forced expiratory volume change relate to lesion development?

Expert B. We need to develop a decent model for lung structure, including zonal conditions.

Expert C. We need multispecies in vitro data to determine tissue sensitivity to ozone exposure. These data would be used as input to test the dosimetry model.

Expert A. We need to compare morphometry and physiology in comparably exposed human and nonhuman exercising subjects. This work should include acute exposure of exercising monkeys and humans and chronic exposure of exercising monkeys, followed by extrapolation.

Information is needed on the effects of increased dose rate due to increased ventilation and on species differences.

Expert C. Monkeys should be included in the dosimetry model.

Expert A. We need to know more about gas distribution within the lung, both at rest and while exercising, and about how the centriacinar lesions affect distribution.

Expert D. We need to know more about the recovery phase. Postexposure repair mechanisms may be more important than the initial damage function.

Graham. How significant are episodes and respites?

Expert E. It is necessary to design experiments to address mechanisms rather than to mimic ambient exposure conditions.

Expert C. We need to determine the significance of background ozone.

It is also necessary to understand how surface area and secretory products affect dosimetry of ozone.

Expert X. Epidemiological studies are needed, especially on the effects of ozone on metastasis.

Expert B. We need to study children growing in environments that are highly oxidizing.

Expert F. We need to study the immune system response to oxidant exposure.

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