Physiologically Based Assessment of Human Exposure to Urban Air Pollutants and Its Significance for Public Health Risk Evaluation

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Exact measurements or modeling of human exposures to environmental pollutants are of crucial importance for a realistic evaluation of public health risks. Current concepts, however, often use assumptions that result in overly conservative assessments of public health risks. Too frequently the dose of the pollutant retained in the body is approximated by oversimplified predictions assuming that all that is inhaled remains in the organism, that pollutant concentrations in various microenvironments are identical to those recorded by remote monitors, that the residence indicates the site where people spend all their time, and that the urban population is continuously exposed to outdoor air for 24 hr/day and 70 years/lifetime. The review shows that in intermittent exposures only a fraction of inhaled toxicants remains in the body, that pollutant concentrations differ largely from one microenvironment to another, and that human activity patterns must be incorporated in every realistic exposure assessments. Specifically, the probability of being exposed to a short peak of ozone is predetermined by variable urban concentrations primarily by the coincidence of exercising outdoors at the time and site of elevated ozone levels. When combined with a physiologically based exposure evaluation, this probabilistic approach provides a scientifically sound estimate of actual occurrences of adverse exposures and a realistic assessment of potential health hazards. — Environ Health Perspect 102(Suppl 4):101–106 (1994).

Key words: urban air pollution, urban air pollution health effects, ozone health effects, urban ozone exposure, physiological exposure models, probabilistic exposure models, exposure models, event effect, adverse exposure

Introduction

In 1970, the U.S. Congress found that the predominant part of the Nation's population is located in its rapidly expanding metropolitan and other urban areas, and that the growth in the amount and complexity of air pollution brought about by urbanization, industrial development, and the increasing use of motor vehicles, has resulted in mounting dangers to the public health and welfare, including injury to agricultural crops and livestock, damage to and deterioration of property and hazards to air and ground transportation (1).

Thus, it enacted legislation intended to protect and enhance the quality of the Nation's air resources so to promote the public health and welfare and the productive capacity of its population (1).

The reasons for public concern were obvious. In 1965 to 1966, air quality data indicated that ambient oxidant levels exceeded 0.16 ppm in the Los Angeles Basin on 70 days/year, and about 63% of people living in the metropolitan Los Angeles area experienced oxidant levels higher than 0.08 ppm more than 50% of the days per year. In 1971, 58% of the total U.S. population resided in areas exceeding the national ambient air quality standard for suspended particulates, and ambient air levels of particulate matter exceeded 150 μg/m³ more often than 5% of all days (2).

On the other hand, the implementation of controls on emission sources between 1970 and 1989 has reduced the U.S. national emissions of volatile organic compounds from 25.0 to 18.5 teragrams/year, carbon monoxide from 101.4 to 60.9 teragrams/year, particulate matter (TSP) from 18.5 to 7.2 teragrams/year, and lead from 203.8 to 7.2 gigagrams/year (3). This represents an unprecedented overall 26 to 96% improvement in these important air quality components that was achieved in spite of a continuing growth of population, energy use, and vehicle miles traveled.

Because of the improved air quality, the evaluation of potential public health hazards from urban air pollution is, therefore, more difficult in the 1990s than it was 20 years ago. With the lower pollution levels, today's assessments require new approaches if the real public health risks are to be assessed and the needs for additional controls evaluated.

The public health risk is usually described as a product of the potency of the toxicant and exposure. A correct description of the latter is, therefore, of crucial importance in all evaluations of the expected risks for public health. This paper will a) review current concepts of exposure definition, b) briefly describe important physiological processes that are involved in the transfer of airborne pollutants into the organism, c) emphasize the stochastic character of the required coincidence of events for adverse human exposure to occur, and d) introduce probabilistic approaches that should result in more realistic exposure estimates.

Current Concepts

Significant progress has been made in the assessment of the health risks from air pollution during the past decade. In 1983, the U.S. Academy of Sciences divided the concept of a science-based risk assessment into four basic components: hazard identification, dose–response assessment, exposure assessment, and risk characterization (4).

The approach emphasized that there are two main components of the risk. The risk is not defined solely by the toxicity or carcinogenicity of pollutants but is equally characterized by an adequate description of human contact with the pollutant (i.e., exposure). Indeed, exposure is a necessary predeterminant of the final outcome; if there is no exposure, no effects can be expected.

Because the term exposure has been interpreted in different ways, the NAS consolidated

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the approach by defining the exposure to a contaminant as
an event consisting of a contact at a boundary between a human and the environment at a specific concentration and for a specified interval of time; the units to express exposure are concentration multiplied by time (5).

This definition of exposure was accepted by the U.S. Environmental Protection Agency (EPA) in 1992 (6), and the Agency describes quantitative exposure by integrating exposure as a function of concentration time

\[
\text{Integrated exposure} = \int_{t_1}^{t_2} C(t) \, dt
\]

where \( C \) is concentration, \( t \) is time, and exposure duration \( t_2 - t_1 \). By convention, the risk is approximated by accepting the principle of Haber's law of equitoxicity (7), which assumes that the effect is independent of pollutant concentrations and proportional solely to the product of concentration and time. This is described by the equation

\[
\text{Effect} = C \times t,
\]

where the effect is equal to the product of concentration \( (C) \) and time \( (t) \). The equitoxicity law has been criticized, however (8), and experimental evidence suggests a limited validity of the formula for breathing organisms (9) as well as exposed plants (10). Moreover, the proposed approach limits the definition of exposure to a contact at a boundary and provides no adequate information on how much of the inhaled pollutant is retained in the organism and what is the resulting absorbed dose to be correlated with the adverse response.

The EPA guidelines, therefore, transform the contact at the boundary into an integrated chemical intake rate and introduce inhalation rate \( [IR(t)] \) as an additional parameter to quantify the delivered dose

\[
\text{Absorbed dose} = \int_{t_1}^{t_2} C(t) \times IR(t) \, dt
\]

where \( C \times IR \) is the concentration of the pollutant in the medium times the intake rate of the medium over time. However, this expression assumes that all that is inhaled is retained in the organism (100% retention). This conservative assumption may not always be correct (11). Consequently, including the inhalation rate into the expression accounts for augmented mass transfer of the pollutant from the ambient air into the organism, and inevitably, for an exaggerated population risk. As shown in the next section, the transfer of the inhaled pollutant in the respiratory system is a complex process and requires pollutant-specific corrections if the net absorbed dose is to be adequately determined and the actual hazard correctly assessed.

The conservatism implied in the many assumptions used in risk evaluation limits more efficient use of these approaches in assessing the actual health risk of air pollution. It introduces systemic errors that can bias the outcome of the evaluation. The limitations are particularly of concern when additional deficiencies of the current approach are considered (e.g., the assumptions that concentrations at remote monitors rather than the breathing zone levels are representative of the individual's microenvironment, that the residence site is the characteristic location where people spend all their time and that a continuous outdoor air contact with the pollutant occurs for 24-hr/day and 70 years/lifetime, etc.). These cumulative errors increase the estimated public hazard and introduce an unacceptable bias into the final assessment of the risk.

Physiological Processes Involved in Pollutant Retention in the Lung

More than adequate information exists on biological processes involved in the uptake of pollutants from the inhaled air in published pharmacological and physiological studies. Similarly, as in physiologically based pharmacokinetics, a physiologically based exposure assessment (PBEA) introducing principles of toxicological and pharmacological science into the evaluation of the actual dose-response mechanisms should be applied in exposure estimates. While mechanistic toxicology and biologically based modeling are effective tools for predicting incidences of adverse responses at various doses of toxins in laboratory animals and people (12), the progress of pharmacokinetic simulations of toxicant disposition, toxicant-target interaction, and tissue responses will remain limited unless similar considerations are given to the exposure process. Too frequently sophisticated pharmacokinetics models are not accompanied by a similar treatment of exposure in routine risk evaluations.

Figure 1 depicts the basic relationship between the exposure and an adverse response. The scheme shows that the conversion of the inhaled toxics by a simple product of concentration and contact time is only a rough approximation of the retained dose determining the final effect. This simplified approach introduces errors unless we consider important parameters of the transcellular transport of pollutants in the assessment scheme.

First, the integrated exposure concept disregards mechanistic differences between respiratory or systemic action of the toxicant. Experimental data demonstrate largely different responses between the concentration-dependent responses of irritant gases directly acting on the respiratory epithelium and between a chronic action of systemic poisons or chemical carcinogens that accumulate in the body (13). Henderson and Haggard (14) pointed out in 1943 that irritating gases and respiratory injury-producing pollutants initiate the adverse responses primarily by the inhaled concentration rather than by an integrated dose from long-term exposures to low concentrations of the same toxics. Numerous experimental data have confirmed this relationship since that time (15,16), but the integrated exposure assessment does not differentiate between these basic mechanisms of toxicant action.

Second, the actual absorbed dose of an inhaled reactive gas such as ozone is not adequately quantified even if expressed as the product of ventilation rate and the inhaled concentration. The scheme in Figure 2 indicates and experimental data confirm that before the inhaled concentration reaches the sensitive walls of the respiratory airways, it encounters a well developed system of effective defense mechanisms. Mainly these include an attenuated ventilation rate and the neutralizing capacity...
of renewable dynamic sinks. In the human lung, these sinks are represented primarily by the increased turnover of disposable alveolar phagocytes, stimulated secretion of mucus produced by the secretory cells of the bronchial walls, or both. It should be noted that both defense mechanisms are extremely reactive and often result in an increased tolerance of the organism to repeated exposures (adaptation).

Even the most elaborate dosimetric models do not recognize the variability and renewable capacity of these defense mechanisms and the level of their impact in preventing the entry of pulmonary irritants into the lung unless their capacity is exceeded. Due to disposal of the reacted products of the pollutant with the mucus or migratory phagocytic cells (that can be fully saturated with the inhaled pollutant), the dose delivered to the peripheral sensitive parts of the respiratory airways is reduced or minimized, if it persists at all. These renewable mucus and phagocytic sinks can irreversibly neutralize reactive gases such as ozone, nitrogen oxides, and other oxidants and provide an effective protection against their effects on respiratory cells. Unfortunately, data on mucus production rates, capacity, or binding power are still scarce and need to be developed if these protective mechanisms are to be quantitatively assessed in dosimetric models.

Third, experimental evidence for nonreactive gases shows that both the mucus layer and the alveolar membrane allow free diffusion of gases in both directions and represent no major barrier to their transfer into or from the circulating blood. However, solubilities of the agent in blood (blood/gas partition coefficients) predetermine whether the inhaled pollutant is retained in the blood compartment and the corresponding depots or excreted with the exhaled air (Figure 3). When a quasi-steady state (saturation) is achieved, no more toxicant is transferred across the alveolar barrier, and the toxicant concentrations in the exhaled air are not different from those inhaled. Contrary to the integrated system predictions, no net intake of the toxicant occurs in the lung at this state, and all that is inhaled is returned back into the ambient air in spite of the continuing boundary contact (exposure). The existence and the kinetics of these mechanisms is well documented for many urban air pollutants (e.g., carbon monoxide, benzene, other industrial solvents, etc.).

Thus, many physiological factors can substantially reduce the net uptake of the pollutant into the organism in spite of the continuing presence of the pollutant in the inhaled air, prolonged contact, or increased ventilation rate. Yet, the conventional exposure models frequently register continuing exposures as a steady uptake of the agent into the organism. This incorrectly increases the absorbed dose and exaggerates the health risks.

The Stochastic Character of Exposure Events
Integrated exposure assessments for population groups are often based on static parameters such as population census, residence sites, etc. and do not adequately recognize the dynamic character of the exposure process. As a result, estimates of the U.S. population living in counties that exceeded the ozone standard in 1990 are estimated to vary between 63 and 140 million people based on the attainment definitions (17). It should be recognized that, similarly, as other random event processes, the occurrence of exposure is basically a stochastic process and is influenced by human behavior. Rigorous deterministic approaches disregard dynamic mobilities of the population as well as of ambient levels and, in most cases, calculate the overall risk as possible exposures per person per year. Even if corrected to include the “sensitive” population, these methodologies have remained in most cases purely approximate estimates that are remote from real-life situations. Thus, in spite of being repeatedly used as a relative index of the risk due to air pollution in a policy context, the exposure estimates continue to be viewed by the technical community as "preliminary in nature because of the considerable uncertainty in inputs regarding human activity and exercise patterns or predicted pollutant concentrations" (18).

The largest use of the simplified deterministic estimates occurred in the development of the scientific basis for the U.S. regulatory process under the provisions of the 1970 and 1977 Clean Air Acts. In the most advanced cases, these exposure models (EPA National Exposure Model [NEM], etc.) describe distributions of exposures in specific population groups by generating randomly selected responses to ozone concentrations exceeding the standard. The probability distribution of the response (triggered by ozone concentrations exceeding the threshold of the specific health point) is frequently calculated by inverting the conditional probability density function according to Bayesian rules and by controlling for possible autocorrelation and systemic seasonal variations (19). The outcome is usually expressed either as the number of possible person–exposures above the standard or the number of persons with at least one excess exposure per year (20).

The uncertainties involved in these risk estimates remain large. Again, all models use fixed-site monitors to represent the quality of air inhaled by the city residents. The models also assume that a small number of fixed-site monitors universally represent the air quality in the entire city area, that the population is adequately characterized by general demographic data (census tracts, etc.), that a simple linear transformation can convert outdoor air quality levels into that corresponding to microenvironments, and that limited human activity studies can be generalized for the entire urban population. The fact that the randomly selected chances do not consider the required coincidence of conditions necessary for exposure occurrence is even a larger concern.

Probabilistic Concepts of Exposure Modeling
Rather than studying the distribution of exposures in static populations, probability models test the chance whether a person selected at random will experience contact with the pollutant given that other required conditions are met.

The approach can be best illustrated with ozone. Ozone is an urban pollutant that is generated by complex interactions of the hydrocarbon emissions with nitrogen oxides and solar radiation. As a secondary pollutant, the ozone concentration depends on the presence of the precursors, UV radiation, and other factors. Consequently, there is a large diurnal variation in ambient ozone levels with
characteristic daily maximum concentrations occurring in the early afternoon (Figure 4). Because the health concerns are concentrated primarily on the highest recorded concentrations or the first violation of the air quality standard (more than 0.125 ppm), there is only a finite interval (window) when such exposures could occur. Differences also exist in the spatial distribution of ozone within the city or county limits. It should be particularly noted that high ozone concentrations exist only in the ambient air outdoors. Ozone levels inside an air-conditioned house are a small fraction of outdoors concentrations. Because human activity patterns indicate that an average person spends no more than 10 to 15% of his or her time outdoors and that the majority of the working population commute large distances to work, the possibility of an exposure to elevated ozone concentrations can occur only when all the conditions for an adverse exposure coincide (i.e., you must be at the site with high concentrations at the time of daily maximum and be outdoors). In addition, ambient air concentrations of ozone must exceed a critical level before the effect is observed. These levels depend on human ventilation rates (physical activities).

Evidence from clinical studies on human volunteers (Table 1) indicates that human organisms tolerate high ozone concentrations (0.5 ppm) when at rest but are sensitive to ozone levels compatible with urban pollution when involved in heavy physical exercise (22). In many cities, this means that an effect-producing exposure can occur in an urban environment only in those exposed persons that intensively exercise. At least four conditions, therefore, must be met if any potentially adverse health effect might occur. Each of these conditions has its own probability, and only when those probabilities coincide is there a chance for an effect event (Figure 5).

The probability of a joint occurrence of mutually independent events is governed by the multiplication rule. This rule states that the probability of simultaneous occurrence of all these conditions is equal to the product of the individual probabilities, under the assumption that the previous individual conditions have already occurred. The probability of an adverse exposure \( P_{EE} \) is then characterized by the expression

\[
P_{EE} = P_{\text{in}} \times P_{\text{peak time}} \times P_{\text{outdoors}} \times P_{\text{exercise}}
\]

showing that the final probability is determined as the product of individual probabilities predicting the outdoor presence \( P_{\text{outdoors}} \) and being at the site with elevated concentrations \( P_{\text{peak}} \), at the time of the concentration peak \( P_{\text{peak time}} \), with the chance of intensive physical exercise \( P_{\text{exercise}} \).

The first stochastic concepts were introduced into exposure modeling by the 1990 modification of the NEM (23). The study simulated exposures using linearized random analysis of personal ozone data collected during the Houston Asthmatic Study. The 1982 Houston conditions (design value of 0.19 ppm with 27.6 days exceeding the standard) were considered roughly equivalent to conditions under which Houston's environment status was determined in 1987 to 1989 (design value of 0.22 ppm ozone with 12.2 days exceeding the

Table 1. Ozone concentrations and physical activity levels at which pulmonary function test decrements occur after 2- to 3-hr ozone exposure (27).

| Concentration, ppm | Conditions                              | Ventilation rate, L/min |
|-------------------|----------------------------------------|-------------------------|
| >0.50             | At rest (sitting)                       | 5–10                    |
| >0.37             | Light exercise (slow walking)          | 10–23                   |
| >0.30             | Moderate exercise (brisk walking)      | 23–43                   |
| >0.24             | Heavy exercise (easy running)          | 43–63                   |
| >0.18             | Very heavy exercise (competitive running) | >63                     |

Figure 4. Typical ozone concentration variation in metropolitan areas of southern California (27).

Figure 5. Probability of an occurrence of adverse exposure to high ozone concentration in urban environments.
The model estimated that the number of persons with daily maximum 1-hr exposure less than 0.12 ppm ozone was in 1982 at the level of 80,813 out of the 2.26 million Houston residents (3.6%).

In 1991, a more complex probabilistic approach was used to analyze the chance of whether a randomly selected member of a population cohort would experience an exposure event by calculating the coincidence of events leading to an adverse exposure. Ozone data from the Houston area and population cohorts with specific activity patterns (home and work districts and commuting groups) were used to estimate the number of person–events (i.e., the probability of being outdoors at the time and site of an ozone peak [0.28 ppm] that occurred in Houston on August 17, 1982 in District 7 at 4:00 P.M.). The person–events were calculated using the following formula:

\[ \text{PERSON–EVENTS}(d, h, w) = \text{POP}(d, h, w) \times \text{EVPROB}(d, h, w) \]

where \( \text{POP}(d, h, w) \) was the population cohort associated with demographic group \( d \), home district \( h \), and work district \( w \) and \( \text{EVPROB} \) was the event probability for the same group and districts. Summing the values of the probabilities over all cohorts produced the number of people who were outdoors in the specified district on the specific day and hour.

The results indicated that out of the studied Houston population of 2.26 million, only 34,145 persons (primarily workers living in the area and nonworking adults of more than 55 years of age) were outdoors in District 7 at the time of the maximum hourly ozone concentration between 4:00 and 5:00 P.M. on August 17, 1982. This represents approximately 1.5% of the Houston population (24). To predict the occurrence of adverse exposures at this site and time in 1982, additional analysis must further estimate the coincidence of the person–events with the possibility of heavy physical exercise (i.e., breathing rate of 45 to 63 L/min, identified by the EPA as the triggering point for adverse exposures at ozone levels higher than 0.24 ppm). The probability is then characterized by

\[ \text{EFFECT EVENT}(d, h, w) = \text{PERSEV}(d, h, w) \times \text{EXERPROB}(d, h, w) \]

where the \( \text{EFFECT EVENT}(d, h, w) \) indicates the probability of adverse exposure, \( \text{PERSEV} \) is the occurrence of person–events, and \( \text{EXERPROB} \) is the product of the population fraction involved in heavy physical exercise and the probability of the exercise coincidence with the ozone peak. In this pilot study, the NEM model value of 36% for the fraction of the heavy exercising (43–63 L/min) population (25) was used as a first order approximation for the heavy exercise group (instead of specific exercise activities of corresponding demographic groups \( d \), at homes \( h \) and working districts \( w \), and the probability of the required coincidence of the physical activity (2 hr out of 12 hr daylight time) with the ozone concentration peak was separately calculated.

Preliminary estimates computed under these assumptions indicate that, contrary to predicted high numbers of adverse exposures expected to occur in the entire studied population by the attainment definition (2.26 million residing in the nonattainment area), this new probabilistic approach restricts the potential for adverse exposures to a much lower fraction of the Houston residents (2034 persons or 0.09%). Because the above calculation was for the ozone peak hour that occurred in 1982 in Houston, the estimate describes only adverse exposures on a single day of the season when ozone concentrations reached a level (0.28 ppm) considered adverse for a population group of substantial size (the heavily exercising persons, which is 36% of all residents). This high ozone level did not reoccur in the studied area during 1982. However, if a similar calculation is made for the few additional days when ozone levels exceeded 0.18 ppm (triggering level for adverse exposures only in very heavy exercising groups with more than 63 L/min ventilation rate), the number of computed adverse exposures is very small (64 events) because the fraction of people involved in these extreme levels of exercise represents no more than 0.26% of the population (25).

Even when all events are summed together (2097), the total number of adverse exposures in Houston in 1982 is orders of magnitude smaller than previous estimates based on the nonattainment area residence and substantially smaller than the predictions of deterministic models. The probabilistic concept permits, therefore, a more realistic assessment of potential health hazards and can dramatically improve public health risk estimates in the regulatory process. These preliminary estimates represent only the first attempt to apply the probability concept in evaluating actual adverse exposure events and need further refinement. Certainly, both the accuracy and validity of the probabilistic methods will be further assured when specific exercise information from activity diaries of the individual demographic cohorts is included in the computation (26). However, assuming that similarly restricted numbers of adverse exposures will be found when the probabilistic concept is extrapolated to other U.S. metropolitan areas, preliminary data presented in Table 2 persuasively illustrate even today that the probabilistic predictions, when compared with previous ozone exposure estimates, are much less conservative and more realistic than the deterministic predictions.

### Conclusions

It can be concluded that:  

(a) The currently used integrated exposure assessment is an overly conservative approach that substantially exaggerates population risks and provides an unusually large margin of safety;  
(b) In contrast, a PBEA considers differences in the mechanisms of action, evaluates physiological protective mechanisms, and permits estimating the net pollutant uptake. When correctly applied, it offers a more realistic measure of the actual absorbed dose and of the relationships between the levels of inhaled pollutants and potential adverse effects; and  
(c) When combined with probabilistic analysis, the physiologically based exposure assessment provides a scientifically sound estimate of the actual occurrences of exposures and potential adverse effects in specific groups of sensitive populations.

The physiologically based probabilistic exposure assessment represents, therefore, progress in the quantitative risk assessment of

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**Table 2.** Ozone exposures in the U.S. population based on different attainment definitions and proposed exposure models.

|                | 3-year average (17) | 1990 (17) | Paul, 1987 total population | Johnson, exercise | This study |
|----------------|---------------------|-----------|----------------------------|-------------------|-----------|
| **Adverse exposure estimates based on residency in nonattainment areas** |                      |           |                            |                   |           |
| Deterministic models (20) | 58%                | 26%       | 15.1%                      | 1.5%              | 0.09%     |
| Probabilistic models (24) | 140 million b       | 62.9 million b | 14.2 million             | 2.7 million c     | 162,000 c |

*Exposure estimates by different exposure models are extrapolated from the Houston analyses under the assumption that the U.S. urban environments (with the exception of southern California) are similar to or better than the 1982 Houston conditions. Based on 240 million U.S. total population. Based on 180 million U.S. urban population.
the potential effects of urban air pollutants on human health and, at the same time, provides a dependable index of the efficiency of applied regulatory measures. The approach will also assure that environmental protection efforts and proposed control technologies are appropriately targeted and offer the best opportunity for an effective reduction of important environmental risks (27).

REFERENCES

1. U.S. Clean Air Act. Title 1, Section 101(a) and (b), as amended December 1970 and August 1977. Report No. 42 U.S.C. 1857 et seq.
2. U.S. EPA. National Air Quality and Emissions Trend Report 1975. Report No. EPA-450/1-76-002. United States Environmental Protection Agency. Research Triangle Park, NC:Office of Air Quality Planning and Standards, 1976.
3. U.S. EPA. National Air Pollution Emission Estimates 1940–1989. Report No. EPA-450/4-91-004. United States Environmental Protection Agency. Research Triangle Park, NC:Office of Air Quality Planning and Standards, 1991.
4. U.S. National Academy of Science, National Research Council. Risk assessment for federal government: managing the process. Washington:National Academy Press, 1983.
5. U.S. National Academy of Sciences, National Research Council. Human exposure assessment for airborne pollutants: advances and opportunities. Washington:National Academy Press, 1991.
6. U.S. EPA. Guidelines for exposure assessment (final draft). United States Environmental Protection Agency. Washington:Office of Health and Environmental Assessment, 1991.
7. Haber F. On the history of the gas wars. In: Fünf Vortrage aus den Jahren 1920–1923. Berlin:Springer Verlag, 1924:76–92.
8. Atherley G. A critical review of time-weighted average as an index of exposure and dose and of its key elements. Am Ind Hyg Assoc J 46:4811–487 (1985).
9. Lazarev NV, Brusilovskaja AI. Dependence of effect of volatile narcotics on exposure and concentration. J Physiol USSR 17:611–619 (1934).
10. Drufuca G, Gugliano M, Torlaschi E. On sulfur dioxide dosages in urban area. Atmos Environ 14:11–17 (1980).
11. Vostal JJ. Physiological basis for ozone air quality standards. In: Tropospheric Ozone: Nonattainment and Design Value Issues. Pittsburgh, PA:Air and Waste Management Association, 1993:53–64.
12. Andersen ME, Krishnan K, Conolly RB, McClellan RO. Mechanistic toxicology research and biologically-based modeling: partners for improving quantitative risk assessment. Chem Ind Inst Tox Activities 12:1–7 (1992).
13. Autrup H. Human exposure to genotoxic carcinogens: methods and their limitations. J Cancer Res Clin Oncol 117:6–12 (1991).
14. Henderson Y, Haggard HW. Noxious gases, 2nd Ed. New York:Reinhold, 1943.
15. Coffin DL, Gardner DE, Sidorenko GI, Pinigin MI. Role of time as a factor in the toxicity of chemical compounds in intermittent and continuous exposures. J Toxicol Environ Health 3:811–828 (1977).
16. Melton CE. Effect of long-term exposure to low levels of ozone: a review. Aviat Space Environ Med 53:105–111 (1982).
17. U.S. EPA. National air quality and emissions trends report, 1990. Report No. EPA-450/4-91-02-023. United States Environmental Protection Agency. Research Triangle Park, NC:Office of the Air Quality Planning and Standards, 1991.
18. Richmond H, McCurdy T. Use of exposure analysis and risk assessment in the ozone NAAQS, review process. Paper No. 88-121.3. Presented at the 81st Air Pollution Control Association Meeting, 19–24 June 1988, Dallas, TX.
19. Hayes SR, Rosenbaum AS, Wallsten TS, Whitfield RG, Winkler RL. Assessment of lung function and symptom health risks associated with attainment of alternative ozone NAAQS. Report No. SYAPP-87/171. San Rafael, CA:Systems Application, 1987.
20. Paul R, Biller WF, McCurdy T. National estimates of population exposure to ozone. Paper No. 87-427. Presented at the 80th Air Pollution Control Association Meeting, 21–26 June 1987, New York.
21. U.S. DHEW. Air quality criteria for photochemical oxidants. United States Department of Health, Education, and Welfare. Washington:National Air Pollution Control Administration, 1970:3–8.
22. U.S. EPA. Review of the National Ambient Air Quality Standards for Ozone: assessment of scientific and technical information (Staff Position Paper). United States Environmental Protection Agency. Research Triangle Park, NC:Office of Air Quality Planning and Standards, 1988:VII–9.
23. McCurdy T, Capel J, Paul R, Johnson T. Preliminary analysis of ozone exposures in Houston using pNEM/O, presented at the 84th Air and Waste Management Association Meeting, 16–21 June 1991, Vancouver, BC.
24. Johnson T, Wijnberg L, Capel JE, Vostal JJ. The use of activity diary data to estimate the probability of exposure to air pollution. In: Proceedings of the Conference on Tropospheric Ozone and the Environment. II. Effects, Modeling, and Controls and the Response of Southern Commercial Forest to Air Pollution, 4–7 November 1991, Atlanta, GA. Pittsburgh, PA:Air and Waste Management Association, 1992:713–724.
25. Whitfield R. Headcount risks of exposure to ozone for heavy and very heavy exercisers. United States Environmental Protection Agency. Research Triangle Park, NC:Office of Air Quality Planning and Standards, 1988.
26. Vostal JJ, Johnson TR. Probability estimates of adverse personal exposures to ozone in metropolitan areas exceeding the national air quality standard. In: Tropospheric Ozone: Nonattainment and Design Value Issues. Pittsburgh, PA:Air and Waste Management Association, 1993:235–254.
27. U.S. EPA. Reducing risk: setting priorities and strategies for environmental protection. Publication No. SAB-EC-90-021. United States Environmental Protection Agency, Scientific Advisory Board, Washington, 1990.