Taylor & Francis
Taylor & Francis Group

Inhalation Toxicology

International Forum for Respiratory Research

ISSN: 0895-8378 (Print) 1091-7691 (Online) Journal homepage: https://www.tandfonline.com/loi/iiht20

Aerosol Synergism and Hydrate Formation—A Possible Connection

Dwight W. Underhill

To cite this article: Dwight W. Underhill (2000) Aerosol Synergism and Hydrate Formation—A Possible Connection, Inhalation Toxicology, 12:sup1, 189-198, DOI: 10.1080/0895-8378.1987.11463192

To link to this article: https://doi.org/10.1080/0895-8378.1987.11463192

Inhalation Toxicology, 12(Supplement 1):189–198, 2000

0895-8378/00 $12.00 + .00

AEROSOL SYNERGISM AND HYDRATE FORMATION—A POSSIBLE CONNECTION

Dwight W. Underhill

School of Public Health, University of South Carolina, Columbia, South Carolina, USA

Earlier experiments using guinea pigs and other laboratory animals have shown that aerosols of sodium chloride potentiate the irritant effects of inhaled sulfur dioxide and formaldehyde. This potentiation was not seen with other vapors such as formic acid and acetic acid; nor was it observed when water-insoluble aerosols were substituted for the sodium chloride. A simple explanation for these results would be that the potentiated vapors dissolved in the hydroscopic particulates and were thereby carried deeper into the respiratory tract. However, such an explanation does not explain the observed difference between potentiated and nonpotentiated vapors. Additionally, the retention time for dissolved vapors is too short to permit the aerosol to transport the dissolved vapor for any appreciable distance. Here it is pointed out that both sulfur dioxide and formaldehyde are hydrated in water solutions to compounds (methylene hydroxide and sulfite, respectively) that have low vapor pressures and are known to decompose only very slowly in water solution. The physical chemistry associated with the formation of these compounds may provide the desired explanation for the observed potentiating effect of inhaled sodium chloride aerosols.

Soon after the highly publicized air pollution episodes in Donora, PA, in 1948 and in London in 1952, there was intense interest in determining how the various components of polluted air, some of which are present in only very low concentrations, interact to produce toxic effects. As both sulfur dioxide (SO_2) and particulate matter were present in these episodes, special importance was given to interactions between these components. A clear statement of this is found in a task force report for the National Institute of Environmental Health Sciences (NIEHS) where it is stated:

> Sulfur dioxide is highly soluble in body fluids. Administered in particle-free air, it is taken up almost entirely by the upper airways (naso and oropharanyx). . . . A large fraction of the accumulation mode of ambient aerosols is soluble and may exist as a solution droplet at low to medium relative humidities. These aerosols absorb sulfur dioxide. When inhaled, they probably carry sulfur dioxide and the products of its combustion with water, beyond the upper airways. These products include sulfite and bisulfite ions. (Nelson et al., 1977, p. 28)

Address correspondence to Dr. Dwight W. Underhill, School of Public Health, University of South Carolina, Columbia, SC 29208, USA. E-mail: dunderhill@sph.sc.edu

Earlier this consideration had important consequences: The U.S. EPA Standards for the *warning, emergency,* and *significant harm levels* of air contaminants included not only levels for SO_2 and particulates separately, but also included the product of their concentrations to account for possible interactions (U.S. EPA, 1971).

EVIDENCE FROM ANIMAL EXPERIMENTS

Of the many experiments to determine the existence of synergistic effects of inhaled gases and vapors, the most extensive, and perhaps the clearest, set of experiments was developed by Amdur, in which she and her co-workers measured the pulmonary resistance and compliance of guinea pigs exposed to various combinations of aerosols and vapors (Amdur & Mead, 1958; Amdur, 1957, 1960, 1966, 1969; Amdur & Underhill, 1968). Most of this work used well-defined components such as a sodium chloride aerosol of known particle size distribution (rather than "smoke" or less well-defined components), giving reproducible experiments in which interactive effects between the aerosol and the inhaled vapor could be discovered and quantitated. Inhaled sodium

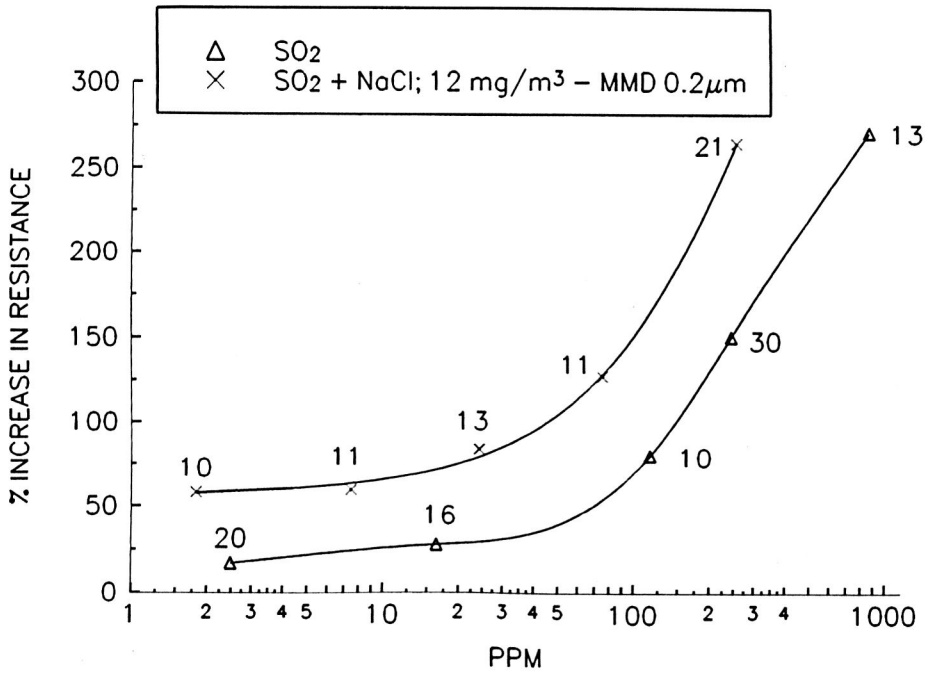

FIGURE 1. Dose-response curves for guinea pigs exposed to sulfur dioxide and to sulfur dioxide plus a sodium chloride aerosol. The number beside each point represents the number of animals exposed to each concentration (results from Amdur, 1957).

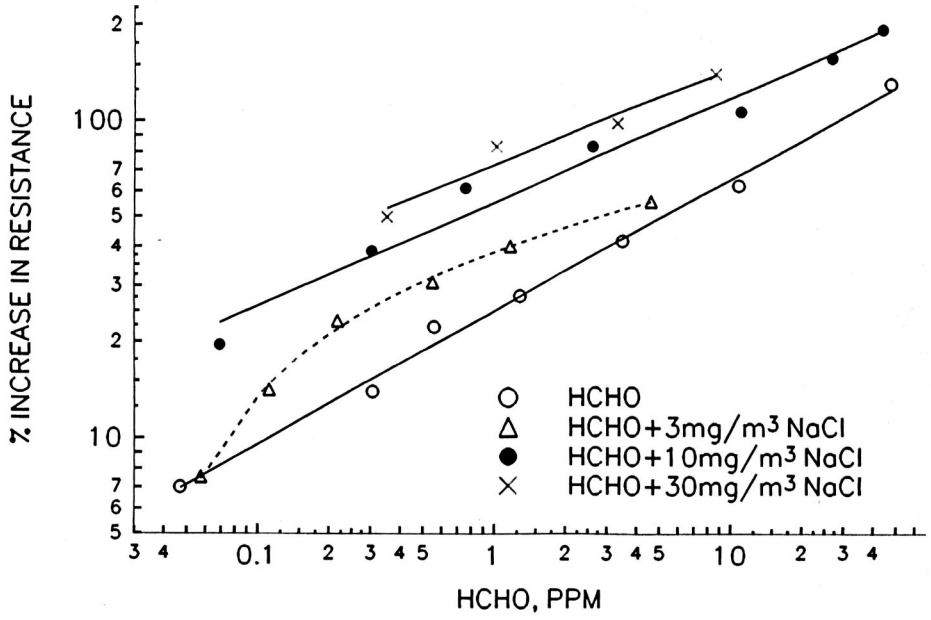

FIGURE 2. Dose-response curve for guinea pigs exposed to formaldehyde and to a combination of formaldehyde and a sodium chloride aerosol (results from Amdur, 1960).

chloride aerosols greatly enhanced the effect of sulfur dioxide on pulmonary resistance. Later a similar effect for sodium chloride aerosols was found with inhaled formaldehyde vapor. In this regard, see Figures 1 and 2, modified from Amdur (1957, 1960).

It is known that a sodium chloride aerosol is hydrated in the respiratory tract, giving a solution in which the vapor might dissolve. A "simple" explanation for the observed synergistic effect between the inhaled vapor and particulates is that some of the vapor was absorbed on the particulates and transported deep into the laboratory animal's lungs. Additional evidence found to support this transport hypothesis includes:

1. Aerosols that are insoluble in water exhibited no synergistic effect with sulfur dioxide. See Figure 3, from Amdur and Underhill (1968).
2. Aerosols of KCl, and NH_4SCN gave a greater synergistic effect with SO_2 than did NaCl. Compared to NaCl, KCl is 1.4 and NH_4SCN 2.1 times as effective in potentiating the guinea pigs' response to sulfur dioxide; 3 *N* solutions of KCl and NH_4SCN dissolve 1.35 and 1.97 times more SO_2 than a 3 *N* solution of NaCl (Amdur & Underhill, 1968).

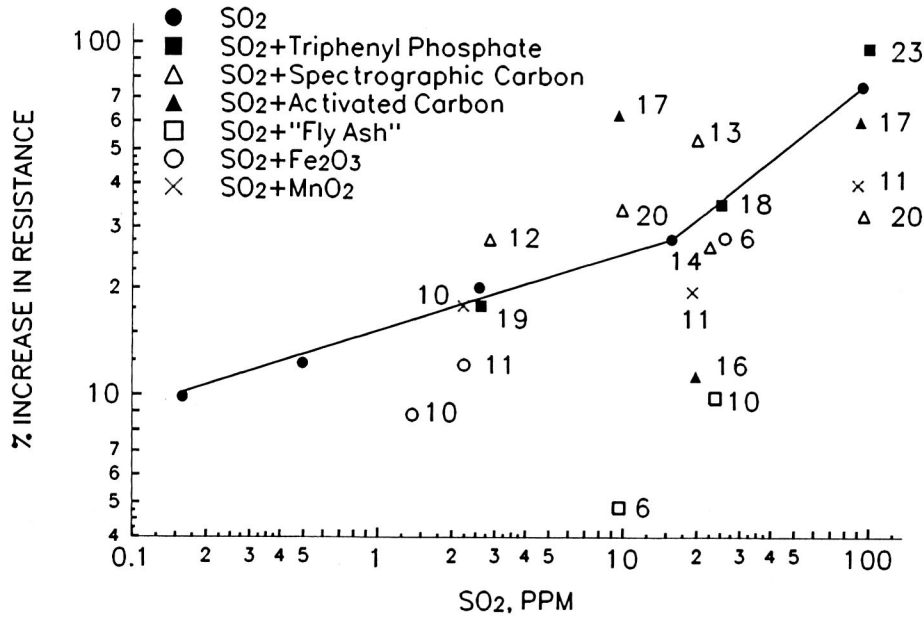

FIGURE 3. Response of guinea pigs to combinations of insoluble aerosols and sulfur dioxide. Number beside each point indicates number of animals in each group. Results from Amdur and Underhill (1968).

DIFFICULTIES WITH THE SIMPLE SOLUTION HYPOTHESIS

There has been controversy regarding the ability of particulate matter to transport vapors in human airways. (Friedlander & Yeh, 1996; Wilson, 1995). In particular, difficulties arise in the concept that observed synergistic effects are solely from the solution of the vapor in the moistened particulates.

1. The synergistic effect is not universal. See Figure 4, which demonstrates that in the same guinea pig preparation as used by Amdur for the SO_2 and the HCHO experiments, inhaled sodium chloride had no measurable synergistic effect with inhaled formic acid vapor. Why then did formic acid, which has a lower vapor pressure in water than sulfur dioxide, show no synergistic effects?
2. The retention time of sulfur dioxide in a droplet is too short to allow the aerosol to retain the dissolved sulfur dioxide or formaldehyde in solution. Assuming that diffusion from the particulate is the rate limiting step in mass transfer, then the fraction of SO_2 remaining at a time t will be (Crank, 1976):

$$\frac{M_t}{M_0} = \frac{6}{\pi^2} \sum_{n=1} \exp\left(-\frac{4\pi^2 n^2 Dt}{d^2}\right)$$

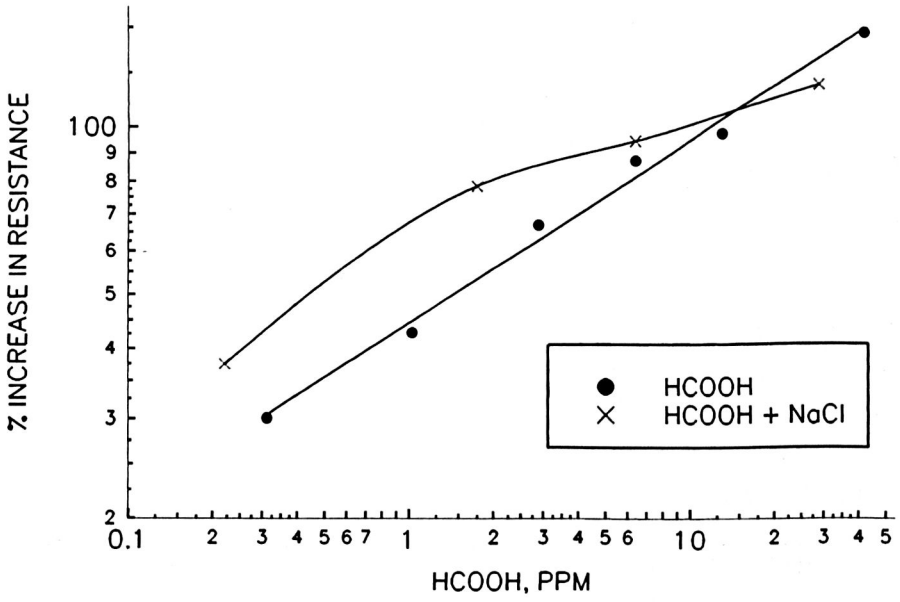

FIGURE 4. Dose-response curves for formic acid alone and for formic acid plus 10 mg/m^2 sodium chloride. The percent increase in resistance at the end of 1-h exposure is the criterion of response, and the concentration is expressed as ppm. Results from Amdur (1960).

where M_0 is the initial amount of absorbed SO_2, M_t the residual SO_2 at time t (same units as M_0), t the time (s), d the particulate diameter (cm), and D the diffusion coefficient for dilute SO_2 in water at room temperature. Assuming $d = 0.2$ μm and $D = 1.77 \times 10^{-5}$ cm^2 s^{-1} (Leaist, 1987), then the time required for loss of half of the absorbed SO_2 is 7×10^{-7} s, which is too short to be important as a transport mechanism through the respiratory tract. This calculation shows that if diffusion is assumed to be the rate-limiting step for mass transfer of vapor from a particulate, then equilibrium is very rapid.

Wexler and Sarangapani (1998) give definitive calculations that if instantaneous equilibrium is assumed, then vapor transport is negligible. The same conclusion can be found through simpler calculations, as follows. Assume a vapor in an aerosol, for which D_m is the diffusion coefficient of the vapor in air (cm^2 s^{-1}), D_s the diffusion coefficient of the vapor in the aerosol particulate (cm^2 s^{-1}), P_c the air–mucus partition coefficient for the vapor (dimensionless), and f the fraction of vapor on the liquid phase (dimensionless). Then the diffusion coefficient for the vapor in the aerosol will be:

$$D_a = (1 - f)\, D_m + f D_s$$

and the partition coefficient ($P_{c\text{-}a}$) for the vapor where the two phases are aerosol versus mucus is:

$$P_{c\text{-}a} = \frac{P_c}{1 - f}$$

With the values usually assumed for f (i.e., <0.1), the partition coefficient and diffusion coefficient for the vapor in the aerosol are very close to those in air, leading to the conclusion that the dynamics of adsorption of the vapor will be essentially the same with inhaled air as with inhaled aerosol. Note that this calculation assumes instantaneous equilibrium between the vapor phase and the particulates.

METHYLENE HYDROXIDE FORMATION AS A MECHANISM FOR THE RETENTION OF FORMALDEHYDE ON AEROSOL PARTICULATES

As a possible mechanism for the physical entrainment of formaldehyde as an aqueous solution by aerosols, we suggest that it is retained as a slowly decomposing hydrate (methylene hydroxide) and offer as evidence the following:

1. Formaldehyde, in dilute water solution, exists primarily (i.e., about 99.9%) as its hydrate. The reaction with water is: $CH_2O + H_2O \leftrightarrow CH_2(OH)_2$.
2. There are many measurements of the rate constants of chemical reactions of dissolved formaldehyde in which the rate-controlling step is the dehydration of methylene glycol. These many experiments are in agreement that at room temperature the half-life for methylene glycol at room temperature in a dilute aqueous solution is about 2.4 min (Le Hénaff, 1963).
3. The vapor pressure of formaldehyde over its dilute water solution is thought to be due to the small fraction of formaldehyde that remains unhydrated and unconverted to the glycol. This is not unreasonable, as the vapor pressure of glycols (as a result of the hydrogen bonding of their two -OH groups) in dilute aqueous solutions are very low.
4. There is experimental evidence that the dehydration of methylene hydroxide can be a rate-limiting factor in the volatilization of formaldehyde from aqueous solutions. Ledbury and Blair (1925), as cited by Walker (1964), were unable to obtain "satisfactory partial pressure values for formaldehyde solutions at low temperatures with scrubbing rates that proved satisfactory at ordinary temperatures. At these temperatures the rate of dehydration [of methylene glycol] was too slow to allow the attainment of equilibrium and the scrubbing rate had to be lowered until equilibrium was the controlling factor" (p. 76). The effect of this rate-limiting dehydration step could be far more pronounced in other situations—such as the volatilization from a submicrometer aerosol, where otherwise the rate of removal might be a matter of a hundredth or a thousandth of a second.

SULFITE FORMATION AS A MECHANISM FOR THE RETENTION OF SULFUR DIOXIDE ON AEROSOL PARTICULATES

There is evidence for a similar rate-limiting dehydration step for sulfur dioxide dissolved in aqueous solutions. Here the reactions are:

$$HSO_3^- + H^+ \xrightarrow{k_1} SO_2 + H_2O$$

$$HSO_3^- \xrightarrow{k_2} SO_2 + OH^-$$

In these equations, the constants k_1 and k_2 are the reaction constants for the formation of hydrated sulfur dioxide from dissolved sulfite. Note that both these reactions bypass the formation of sulfurous acid; there is, despite what many chemists still may believe, very strong spectrographic evidence that unionized H_2SO_3 is not present in aqueous solutions of SO_2 (ley & König, 1938).

The question here is the speed of the conversion of sulfite ion to sulfur dioxide. Wang (1963) showed that this reaction rate is sufficiently slow to be measured in terms of minutes. His procedure was to inject a tracer in the form of $NaH^{35}SO_3$ into a solution containing $^{32}SO_2$, H_2O, and $NaH^{32}SO_3$, which had been allowed to reach equilibrium under controlled conditions of temperature, pH, and pressure. At intervals he flashed the SO_2 out of samples of this solution. The ratio of $^{35}SO_2$ to the total SO_2 gave the transfer of ^{35}S between the sulfite and the dissolved SO_2. At the time of initial transfer, none of the ^{35}S was present as sulfite; at equilibrium, there was equal distribution of ^{35}S and ^{32}S between the sulfite ion and SO_2. Figure 5 shows the results from one such experiment. There the ratio of $^{35}S/^{32}S$ compared to the equilibrium ratio of $^{35}S/^{32}S$ as a function of time is plotted on a semilogarithmic plot. The important factor to note in this plot, as well in his other data, is that the half-life for this transfer is nearly a minute. The relevance of this experiment is that the rate constant is measured in tens of seconds, whereas the time required to transport an aerosol from the ambient atmosphere to the alveoli is measured in seconds or a fraction of a second. The slow conversion of the sulfite ion to dissolved sulfur dioxide gives a plausible mechanism for the transport SO_2 as sulfite on hygroscopic aerosols.

FORMIC ACID

Indirect evidence for the hydration hypothesis is that, as far as is known, the rate constant k for the reaction between formate ion and the hydronium ion

$$COOH^- + H^+ \xrightarrow{k} HCOOH$$

is so rapid that a case cannot be made for this reaction being a rate-limiting step. In this regard, Delahay and Vielstich (1955), using classical polarographic techniques, found very rapid rate constants for both the association and dissociation of formic acid in aqueous solution.

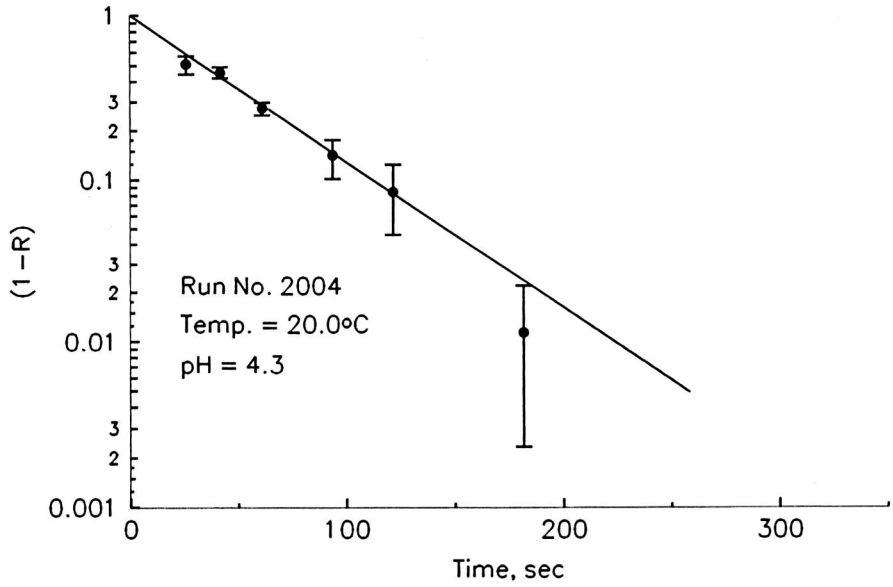

FIGURE 5. Equilibrium between labeled and stable sulfite ion in aqueous solution. The *x* axis gives equilibrium time in seconds. The factor *R* in the *y* axis gives the ratio of ^{35}S in the counting gas at time *t* to that at isotopic equilibrium. Results from Wang (1963).

EXPERIMENTAL EVIDENCE FOR AEROSOL TRANSPORT

Ichioka (1972) used a series of tubes 9 mm in diameter, 100 ml long, lined internally with moistened filter paper to model the respiratory tract. Through this system he passed dilute SO_2 alone, and SO_2 plus a NaCl aerosol. The SO_2 in the effluent from these wetted-wall tubes was collected in a bubbler. In reviewing these experiments as published, a major difficulty arises in that mass transfer calculations show that the total of SO_2 passing his system differs by factors between 3 and 5 from the amount of SO_2 absorbed on the wetted walls and in the bubbler. But even though this experiment can be severely criticized, the percent of the SO_2 passing through the wetted-wall tubes was less than 3% in the absence of a NaCl aerosol; adding a NaCl aerosol increased this fraction to 12%. This study, even though the mass transfer balance is flawed, seems to give credence to the hypothesis that the presence of a NaCl aerosol increases the transport of SO_2 through systems such as the respiratory tract.

PROPOSALS FOR FUTURE RESEARCH

The purpose of this note is to give plausible mechanisms for the transport of vapors by aerosols. Should the chemical reactions described here—the

dehydration of methylene hydroxide and the neutralization and dehydration of sulfite ion—prove to be valid mechanisms for the retention of HCHO and SO_2 on hydroscopic particles, then tests with laboratory animals could be used to determine the importance of this means of transport. For example, the unattached HCHO or SO_2 could be stripped from the gaseous phase, and the irritancy of the compounds attached to aerosol particulates could be measured directly in tests with laboratory animals or human subjects. The known rate of dehydration may also prove helpful in establishing whether the experiments carried out with guinea pigs, with their much smaller respiratory tract, have much relevance to human exposures. In any case, the physical chemistry for the mechanisms proposed here has been in the literature for a number of years. The purpose of this note is to spur research to determine if aerosol physicists and pulmonary toxicologists will find this information useful in trying to understand aerosol transport of absorbed vapors and its relevance to the still important problem of air pollution.

REFERENCES

Amdur, M. O. 1957. The influence of aerosols on the respiratory response of guinea pigs to sulfur dioxide. *Am. Ind. Hyg. Q.* 18:149–155.

Amdur, M. O. 1960. The response of guinea pigs to inhalation of formaldehyde and formic acid alone and with a sodium chloride aerosol. *Int. J. Air Pollut.* 3:201–220.

Amdur, M. O. 1966. Respiratory absorption data and sulfur dioxide response curves. *Arch. Environ. Health* 12:729–732.

Amdur, M. O. 1969. Toxicologic appraisal of particulate matter, oxides of sulfur, and sulfuric acid. *J. Air Pollut. Control Assoc.* 19:638–644.

Amdur, M. O., and Mead, J. 1958. Mechanics of respiration in unanesthetized guinea pigs. *Am. J. Physiol.* 192:364–368.

Amdur, M. O., and Underhill, D. W. 1968. The effect of various aerosols on the response of guinea pigs to sulfur dioxide. *Arch. Environ. Health* 16:460–468.

Crank, J. 1976. *The mathematics of diffusion.* Oxford: Clarendon Press.

Delahay, P., and Vielstich, W. 1955. Kinetics of the dissociation of weak acids and bases—Application of polarography and voltammetry at constant current. *J. Am. Chem. Soc.* 77:4955–4958.

Friedlander, S. K., and Yeh, E. K. The submicron atmosphere aerosol as a carrier of reactive chemical species: case of peroxides. *2nd Colloq. Particulate Air Pollution and Health*, Park City, UT, May, 1996.

Ichioka, M. 1972. Model experiments on adsorbability of the airway mucous membrane of SO_2 and NO_2 bases. *Bull. Tokyo Med. Dent. Univ.* 19:36–75.

Leaist, D. G. 1987. Diffusion of aqueous carbon dioxide, sulfur dioxide, sulfuric acid, and ammonia at very low concentrations. *J. Phys. Chem.* 91:4635–4638.

Ledbury, W., and Blair, E. W. 1925. Partial formaldehyde vapor pressures of aqueous solutions of formaldehyde. *J. Chem. Soc.* 127(33-7):28345.

Le Hénaff, P. 1963. Sur la vitesse de dehydration du methylene glycol en formaldehyde. *Comptes Rendus* 256:1752–1754.

Ley, H., and König, E. 1938. Spectra of solutions of important acids of the sulfur group. *Z. Phys Chem. B* 41:365–387.

Nelson, N. 1977. *Human health and the environment—Some research needs.* DHEW Publication NIH 77-1277, Washington, DC: Department of Health Education and Welfare.

U.S. Environmental Protection Agency. 1971. National primary and secondary ambient air quality standards. *Fed. Reg.* 36:8186.

Walker, J. F. 1964. *Formaldehyde*, 3rd ed. American Chemical Society, Monograph Series 159. Huntington, NY: Robert E. Krieger.

Wang, J. C. 1963. Kinetic study of sulfur dioxide in aqueous solution using radioactive tracer. PhD thesis, University of Texas, Austin (University Microfilms 64-117).

Wexler, A. S., and Sarangapani, S. 1998. Particles do not increase vapor deposition in human airways. *J. Aerosol Sci.* 29:197-204.

Wilson, W. E. 1995. Labile species in particle-bound water. *Inhal. Toxicol.* 7:795.