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Mobile-Source Air Toxics: A Critical Review of the Literature on Exposure and Health Effects

Acrolein

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Acrolein

INTRODUCTION

Acrolein (CAS Registry Number 107-02-8; C_3H_4O; molecular weight = 56.1) (Figure 4), also known as 2-propenal, is a volatile, highly electrophilic α,β-unsaturated aldehyde with a boiling point of 53°C. It is highly reactive in air and has a half-life of 1 day. It is commonly found in smoke from burning organic matter. Acrolein is released into the ambient air through the combustion of gasoline, oil, coal, and tobacco. It is also a by-product of fire and of 1,3-butadiene reactions in the atmosphere. In manufacturing processes, it is used to produce acrylic acid, which is used in turn to make acrylate polymers. In addition, it is used as a biocide to control aquatic flora and fauna. Acrolein is a metabolite of the cancer-chemotherapy agent cyclophosphamide.

At one atmosphere pressure and 25°C, 1 ppm acrolein is equivalent to 2.33 mg/m^3.

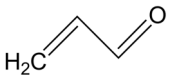

Figure 4. Structure of acrolein.

BENCHMARK LITERATURE

The following evaluation of research literature on acrolein is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from the EPA (2000c), the Agency for Toxic Substances and Disease Registry (ATSDR 2005c), and Weisel and colleagues (2005). Personal-exposure data are from a large study funded by HEI (Weisel et al. 2005). Data on outdoor and indoor residential concentrations of acrolein are also from the HEI study (Weisel et al. 2005) and represent one of the largest data sets available. Data summaries from the EPA Air Quality System database (2004a) were used to calculate urban, suburban, and rural concentrations of acrolein.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

EXPOSURE

SOURCES AND EMISSIONS

According to the National Air Toxics Assessment (NATA), in the U.S., on-road mobile sources account for 13.7% of acrolein emissions nationwide, 24.4% of all emissions in urban areas, and 5.4% of all emissions in rural areas (EPA 2006b). The oxidation of atmospheric 1,3-butadiene, which is emitted from motor vehicles, is an important source of acrolein in ambient air (ATSDR 2005a,c). The concentration of acrolein in motor vehicle exhaust is 0.47 mg/m^3 (Swarin and Lipari 1983). An important indoor source of acrolein is cigarette smoke (EPA 2000c; ATSDR 2005c). Acrolein is present in the vapor phase of cigarette smoke at 8.2 µg per 40-mL puff (Feron et al. 1978). Acrolein concentrations in mainstream smoke have been estimated to range from 3 to 220 $µg/m^3$ per cigarette (ATSDR 2005c) and in sidestream smoke from 100 to 1700 $µg/m^3$ (ATSDR 2005c). Proximity to a smoker or to enclosed spaces where smoking occurs might represent potentially important acrolein exposures.

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Relatively little air-monitoring data exist for acrolein, in part because of its high reactivity, its short half-life (1 day), and measurement limitations. It has been suggested that some of the current methods for measuring acrolein have poor sensitivity, selectivity, and reproducibility. These limitations have in turn led to the speculation that concentration data reported in the literature might underestimate actual exposure concentrations. The limitations are associated with the use of sorbent-filled cartridges containing carbonyl-derivatizing agents for the collection of unsaturated carbonyls such as acrolein. The limitations include instability of the dinitrophenylhydrazine (DNPH)–acrolein hydrazone during collection and storage, poor chromatographic separation of complex carbonyl mixtures found in ambient and indoor air, and potential ozone interference (Seaman et al. 2006; Cahill et al. in press). A sampling method recently developed and used to monitor ambient urban, residential, and personal-exposure concentrations of acrolein might have overcome these limitations and might be yielding more reliable data (Weisel et al. 2005).

Table 3 and Figure 5 show the range of mean and maximum concentrations of acrolein in μg/m^3 measured outdoors, indoors, and by personal-exposure monitoring. Outdoor locations include urban, urban roadside, urban in-vehicle, suburban, and rural environments. Indoor spaces include residences and schools. Personal-exposure data are reported for adults and children. Sampling times ranged from 1 hour (Destaillats et al. 2002; Fitz et al. 2003) to 6 days (Sawant et al. 2004), with sample-averaging times ranging from a few hours (e.g., Destaillats et al. 2002) to 1 year (e.g., Sax et al. 2004). The number of measurements per study, from which the mean and maximum concentrations were determined, ranged from a low of 6 for a tunnel study (Destaillats et al. 2002) to a high of 2574 for the combined urban–suburban–rural category from the Air Quality System data set (EPA 2004a). The 2574 individual

Table 3. Acrolein Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (μg/m^3)		Citations	Comments
			Mean	Maximum		
Outdoor Areas						
Urban						
	27 averages*	Yearly	0.6	1.96**	EPA 2004a	
	—	Yearly	0.13	—	EPA 2006b	Model
	395	Yearly	6.3	11.9	Sax et al. 2004	Summer and winter
Urban in-vehicle						
	31	60–90 hr	—	0.5	Fitz et al. 2003	Bus
	50	7–15 hr	0.04	1.0	Riediker et al. 2003	Patrol cars
Urban roadside						
	6	4 hr	—	0.14	Destaillats et al. 2002	
	8	2 hr	—	0.6	Grosjean and Grosjean 2002	Tunnel
	10		—	0.31	Grosjean and Grosjean 2002	Tunnel
Suburban						
	30 averages*	Yearly	0.8	2.33**	EPA 2004a	
Rural						
	—	Yearly	0.03		EPA 2006b	Model
	10 averages*	Yearly	0.5	1.8**	EPA 2004a	
Indoor Spaces						
Residences						
	30	100 min	< 2.0	< 2.0	Feng and Zhu 2004	
	14	24 hr	< 0.1	< 0.1	Reiss et al. 1995	Winter
	26	24 hr	< 0.1	< 0.1	Reiss et al. 1995	Spring
	83	6 days	1.4	3.6	Sawant et al. 2004	
	62	24 hr	4.1***	21.0	Sheldon et al. 1992	
	398	2 seasons	1.7	14.8	Weisel et al. 2005	Summer and winter
Schools						
	28	6 days	1.2	2.1	Sawant et al. 2004	Classrooms
Personal Exposures						
	409	2 days	12.9	11.2	Weisel et al. 2005	Adults
	169	2 days	10.9	> 8.3$^+$	Weisel et al. 2005	Children

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 2,574 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average; *** = median; $^+$ 99th percentile = 504 μg/m^3 (this appears to be an outlier, so 95th percentile is used).

measurements contained in this data set were broken down as mean urban, suburban, and rural concentrations. The mean urban concentration of 0.14 μg/m^3 and the mean rural concentration of 0.04 μg/m^3 shown in Figure 5 were estimated by using the NATA model (EPA 2006b).

Only seven of all the studies reviewed reported concentrations of acrolein in ambient air. Although data are limited, there does appear to be an increasing gradient in mean and maximum concentrations from rural to suburban to urban, with mean values ranging from 0.5 to 6.3 μg/m^3 and maximum values ranging from 1.8 to 11.9 μg/m^3. The NATA reported a nationwide estimated mean concentration of 0.11 μg/m^3, with estimated concentrations of 0.13 μg/m^3 and 0.03 μg/m^3 for urban and rural areas, respectively (EPA 2006b). These estimated concentrations are an order of magnitude lower than measured concentrations. Although limited, the data for urban roadside and urban in-vehicle acrolein measurements suggest that exposures in these environments are considerably lower at both mean and maximum concentrations than in other outdoor spaces, residences, schools, or personal exposures. Measurements from tunnel studies indicate that acrolein concentrations are surprisingly low (< 0.6 μg/m^3), given that on-road mobile sources account for 24% of urban acrolein emissions.

Six studies reported acrolein concentrations in residences, and one reported concentrations measured in school classrooms. In three of the six residential studies, concentrations were below the limit of detection. In the remaining three—one of which used a collection system designed to overcome the limitations of existing methods (Weisel et al. 2005)—residential concentrations were similar to outdoor concentrations, with mean concentrations of less than 10 μg/m^3 and one maximum concentration of 21 μg/m^3. Two of the studies were conducted in households of nonsmokers (Sheldon et al. 1992; Sax et al. 2004). Although environmental tobacco smoke is an important source of acrolein indoors, none of the studies reviewed here included households of smokers. The one study reporting classroom measurements found acrolein concentrations to be low, with a mean concentration of 1.2 μg/m^3 and maximum concentration of 2.1 μg/m^3 (Sawant et al. 2004).

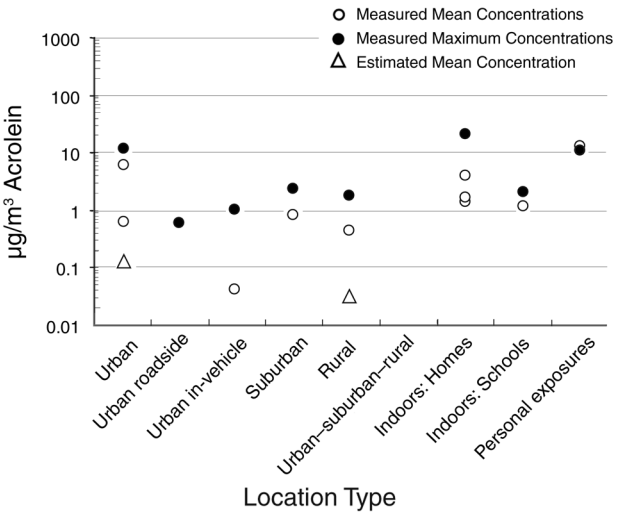

Figure 5. Concentrations of acrolein (μg/m^3) at various locations. Data for figure are from Table 3.

The one study that used the improved collection system made extensive measurements of personal acrolein exposure as well as indoor residential and outdoor exposure for a group of nonsmoking adults and children (Weisel et al. 2005). Mean and maximum personal exposures for adults tended to be similar and in the range of 11 to 12 μg/m^3. Mean personal-exposure concentrations were twice those measured outdoors and six times those measured inside the residence. Maximum personal-exposure concentrations tended to be similar to those measured both outside and inside the home. The study compared two types of samplers used to measure concentrations of acrolein (an active sampler with DNPH-coated filters and a passive sampler with dansylhydrazine-coated filters). In the study (Weisel et al. 2005) and in two prior studies (Zhang et al. 1994; Zhang et al. 2000), the samplers containing DNPH-coated collection media were found to underestimate acrolein concentrations by a factor of two. Many of the available data on acrolein concentrations were collected using DNPH-coated samplers like these, leading to the conclusion that measurements made with such samplers might be underestimating acrolein concentrations.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

A survey of the published literature found only one study with a measurement of detectable ambient acrolein concentrations outside the U.S. This measurement (1.48 μg/m^3 in a bus station in China) was in the range of measurements obtained in the U.S. (Feng et al. 2005).

TEMPORAL TRENDS

At present, the limited number of measurements and the unreliability of sampling methods make an assessment of temporal trends in ambient concentrations of acrolein impossible.

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

Inhalation is the main route of exposure to acrolein. The metabolism of acrolein in rats has been described (Draminski et al. 1983) (Figure 6). Acrolein reacts readily with glutathione, depleting this antioxidant in tissues, and is excreted as a mercapturic acid in the urine. This is the major pathway for detoxification. Acrolein can be oxidized in the liver by alcohol dehydrogenase to acrylic acid or by liver or lung microsomal cytochrome P450s to form the epoxide glycialdehyde, which is hydrolyzed in turn to form glyceraldehyde.

BIOMARKERS

No reliable biomarkers have been reported for either exposure to or effects of acrolein (ATSDR 2005c). Early studies suggested that 3-hydroxypropyl mercapturic acid in urine might be useful as a biomarker for acrolein, but it did not correlate well with exposure (Alarcon 1976).

NONCANCER HEALTH EFFECTS

The LC_{50} for 4- to 6-hour inhalation exposures of acrolein in mice, rats, rabbits, and guinea pigs is approximately 23 mg/m^3 (Kane et al. 1979; Beauchamp et al. 1985). The major toxicologic properties of the compound are that it is extremely irritating and that it binds irreversibly to the tissues of the respiratory tract when inhaled. For

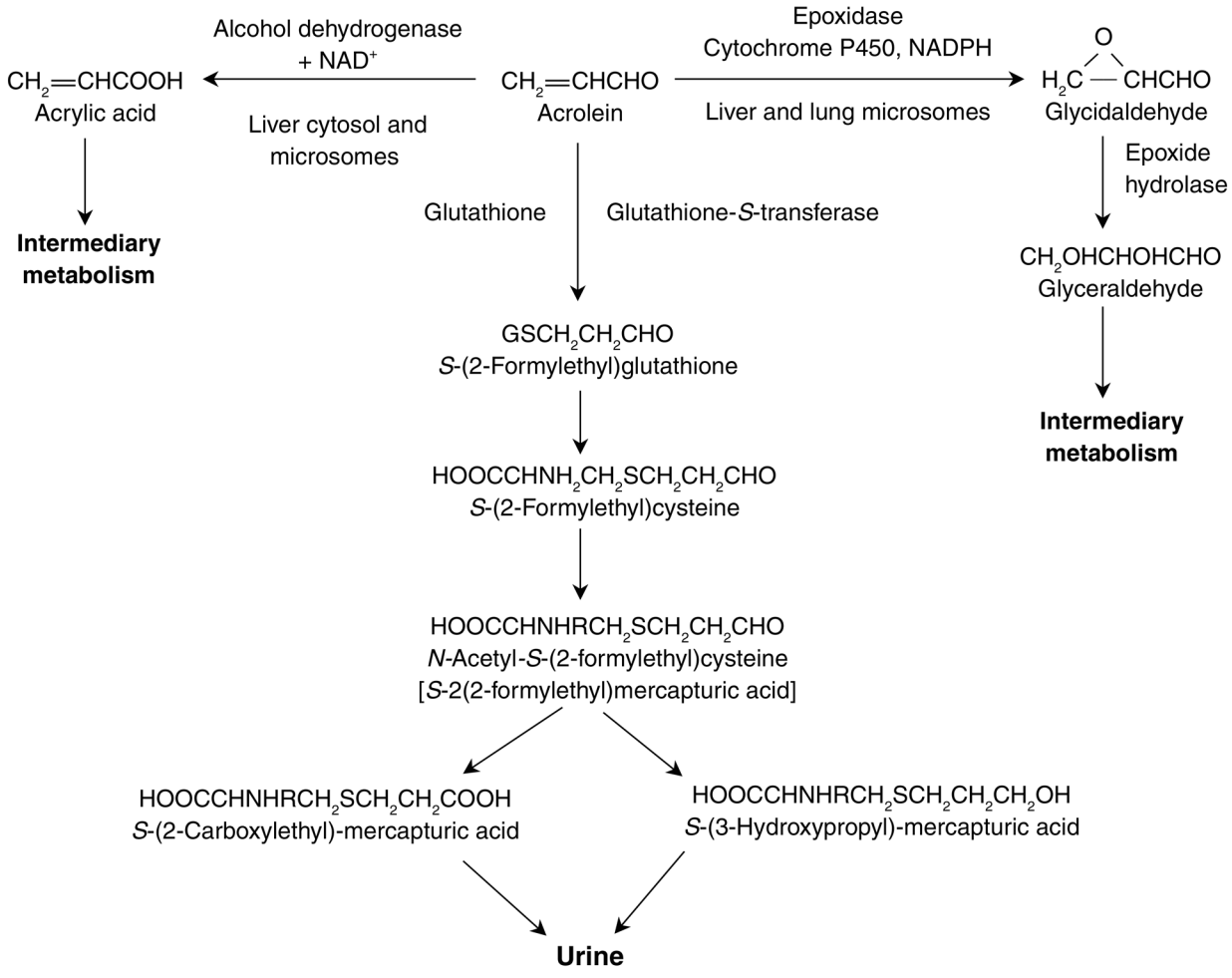

Figure 6. Metabolic pathway of acrolein. R = COCH. (Modified from Draminski et al. 1983, with the permission of Springer Science and Business Media.)

this reason, inhaled acrolein does not distribute well to other organs. Acrolein inhibited the respiratory rate in mice at a concentration of 1.6 mg/m^3 (Steinhagen and Barrow 1984) and in rats at a concentration of 14 mg/m^3 (Babiuk et al. 1985). As reviewed by the World Health Organization (WHO 1992; International Agency for Research on Cancer [IARC] 1995), repeated inhalation of acrolein in rats, guinea pigs, rabbits, Syrian hamsters, monkeys, and dogs caused reduction in body weight and interference with pulmonary function as well as a variety of histopathological changes in the nose, airways, and lungs. The exposure concentrations ranged from 0.5 to 11 mg/m^3 for periods of up to 13 weeks.

In obligate nose breathers, the nose was a sensitive target organ because of the reactive nature of the compound. In all species studied, neutrophilic infiltration and focal squamous-cell hyperplasia and metaplasia were observed in the upper respiratory tract. Repeated exposure of dogs to 4 mg/m^3 for 24 hours/day for 90 days resulted in confluent bronchopneumonia. Guinea pigs and rats showed focal liver necrosis after similar exposures to 2 mg/m^3. In rats and rabbits exposed to acrolein for 13 weeks at 1 to 11 mg/m^3, tracheal inflammation, mucous-gland hyperplasia, epithelial metaplasia, bronchiolitis, accumulations of alveolar macrophages, and focal interstitial pneumonitis (at high doses only) were observed (Feron et al. 1978). More recent studies have focused on the molecular interactions of acrolein with tissues (Kehrer and Biswal 2000). At low doses, as would be expected in tissues after inhalation exposure, acrolein inhibited cell proliferation without causing cell death and might have enhanced apoptosis induced by other toxins. Kehrer and Biswal suggested that the acrolein-mediated decrease in cell proliferation was caused by changes in expression of growth- or stress-related genes or transcription factors secondary to the depletion of glutathione known to be caused by acrolein. Acrolein was ciliostatic in rabbit tracheal slices (Dalhamn and Rosengren 1971). No reproductive toxicity was seen in rats or rabbits treated with acrolein by gavage.

GENOTOXICITY

In Vivo

No studies have reported genotoxic effects of acrolein in humans or animals by any route of exposure (ATSDR 2005c). Acrolein did not induce DNA damage in rats or dominant-lethal mutations in mice treated in vivo (Epstein et al. 1972). Acrolein induced both somatic and germinal mutations in insects (IARC 1995).

In Vitro

Acrolein binds chemically with proteins and DNA in vitro, but DNA adducts have not been detected in exposed animals (Nelsestuen 1980; Chung et al. 1984). Acrolein induced DNA damage and mutation in bacteria (IARC 1995). Based on a recent summary of the genotoxicity of acrolein (ATSDR 2005c), acrolein is weakly mutagenic in bacteria without an exogenous metabolism system and nonmutagenic in bacteria with an exogenous metabolism system. In yeast, acrolein was not mutagenic unless there was exogenous metabolism.

In cultured mammalian cells, acrolein induced gene mutation, sister-chromatid exchange, and DNA damage in some, but not all, mammalian-cell test systems (ATSDR 2005c). It also acted as a potent inhibitor of the DNA repair enzyme O^6-methylguanine-DNA methyl transferase (ATSDR 2005c).

Acrolein forms DNA adducts on synthetic oligonucleotides at deoxyguanosine sites, and this lesion might be responsible for mutagenic activity (D'Isa et al. 2004). There were many of these adducts on telomeric repeat regions, and preliminary results suggested that acrolein can form adducts on synthetic oligodeoxyribonucleotides containing such telomeres (D'Isa et al. 2004).

Acrolein causes DNA adducts in human tissues and this adduct formation is related to exposure—presumably to cigarette smoke. Nath and Chung (1994) developed a sensitive ^{32}P-postlabeling method combined with high-performance liquid chromatography to detect exocyclic adducts resulting from binding at two sites of bases involved in the hydrogen bonding that maintains the double-helical structure of DNA. They found 1,N^2-propanodeoxyguanosine adducts of acrolein and crotonaldehyde in human liver DNA; the number of acrolein adducts detected was 0.3 to 2.0 adducts in 10^6 guanine bases, which was considered to be a very high concentration and indicative of exposure to cigarette smoke. In another study, Nath and colleagues (1998) noted that acrolein was present in cigarette smoke at 100 to 1000 µg/cigarette (depending on the brand) and in automobile exhaust, and that acrolein could also be a product of endogenous lipid peroxidation. They analyzed the aforementioned adducts in gingival DNA from 11 smokers and found that mean acrolein-derived 1,N^2-propanodeoxyguanosine concentrations were 1.36 ± 0.90 µmol/mol guanine in the 11 smokers compared with 0.46 ± 0.26 µmol/mol guanine in 12 nonsmokers (P = 0.003). Cohen and colleagues (1992) reported that acrolein induced bladder cancer in rats when 2 mg/kg body weight of acrolein was injected intraperitoneally twice a week for 6 weeks, followed by

administration of uracil as 3% of the diet for 20 weeks (18 of 30 rats, compared with 8 of 30 rats exposed to control solvent). An identical 6-week acrolein protocol followed by a control diet produced no tumors. A 26-week acrolein exposure protocol had to be stopped at 21 weeks because of severe toxicity. Most important, Feng and colleagues reported that in cultured cells from normal human bronchial epithelia, acrolein formed DNA adducts on the p53 tumor-suppressor gene at mutational hot spots at CpG sites where G→T transversions occur (Feng et al. 2006). In addition, acrolein can form DNA adducts at p53 codon 249, which is a lung cancer mutational hot spot that does not form adducts with benzo[*a*]pyrene. Acrolein greatly reduces nucleotide-excision repair capacity, the major repair pathway for bulky DNA damage.

CANCER

In Vivo

Acrolein is metabolized in vitro by liver and lung microsomes to glyceraldehyde, which is carcinogenic to mice after skin application and to mice and rats after subcutaneous injection, producing tumors at the site of application (IARC 1987). In three carcinogenicity studies of orally administered acrolein (two in rats and one in mice), no treatment-related increases in tumor frequency were observed (IARC 1987). One inhalation study was conducted in Syrian hamsters for 52 weeks (with an exposure concentration of 0 or 9 mg/m^3); no increase in neoplasia was observed (IARC 1987). In another study of mice, application of acrolein to skin did not increase the number of papillomas (IARC 1995). An increased incidence of urinary bladder papillomas was observed in rats receiving intraperitoneal injections of acrolein in combination with uracil in the diet; no papillomas were observed with acrolein treatment alone (IARC 1987). In a study at the National Center for Toxicological Research, 150 or 75 nmol acrolein was injected intraperitoneally twice into neonatal B6C3F1 mice. Liver adenomas were observed in 5 of 96 male mice injected with the 75 nmol dose. These results showed that neonatal mice were relatively insensitive to acrolein (Von Tungeln et al. 2002).

HUMAN HEALTH

CANCER

No studies of the carcinogenicity of acrolein in human populations were identified.

NONCANCER HEALTH EFFECTS

Acrolein is a respiratory irritant starting at concentrations as low as 700 µg/m^3 in humans and is reactive in cell cultures; it causes growth inhibition, increased cell-membrane permeability, and apoptosis (Feron et al. 1978; Kehrer and Biswal 2000; Finkelstein et al. 2001; Biswal et al. 2002). Acrolein is highly reactive with sulfhydryl groups (cysteine, histidine, and lysine) and is endogenously produced during lipid peroxidation. Studies of firefighters exposed to wood smoke in prescribed burns in the western U.S. found a work-shift effect of −125 mL for FEV_1 (forced expiratory volume in one second). However, the presence of acrolein in smoke was correlated with that of other compounds, making it impossible to distinguish the effects of the acrolein (Slaughter et al. 2004).

Acrolein can inhibit human alveolar-macrophage release of interleukin (IL)-1β, IL-12, and tumor necrosis factor-α (TNF-α) after in vitro exposures, probably by inhibiting effects on nuclear factor-κB (NFκB) (Li L et al. 1999). In cell culture exposures, 5 to 25 µM acrolein reduced levels of IL-8 mRNA and protein, apparently through effects on NFκB (Valacchi et al. 2005). Earlier studies (Cantral et al. 1995) showed that cigarette smoke inhibited the ability of cultured normal human bronchial epithelial cells to attach to the extracellular matrix and to migrate in response to chemotactic stimuli. When such cells were exposed to acrolein concentrations (5, 10, or 25 µM) chosen to mimic doses that lung epithelial-lining fluid would receive after exposure to mainstream or sidestream tobacco smoke, a dose-related decline in IL-8 protein and mRNA and subsequent TNF-α stimulation were observed. Because IL-8 has NFκB binding sites on its promoter, the authors speculated that these effects were mediated through the oxidation of cysteines in the DNA-binding domain of NFκB, thus affecting DNA-binding capacity. Acrolein also caused an increase in the inhibitory IKKβ, which might prevent the release of NFκB from the cytoplasm to the nucleus, and inhibited activated protein-1 activity in A549 lung-adenocarcinoma cells because of altered glutathione imbalance (Biswal et al. 2002). Thioredoxin also contains thiol groups and was reduced in A549 cells after exposure to acrolein (Yang et al. 2004).

Acrolein causes apoptosis of human alveolar macrophages (Li L et al. 1997) and bronchial epithelial cells when administered in vitro. These effects occur through the mitochondrial pathway by liberating cytochrome c, activating the initiator caspase-9, activating the effector caspase-7, and inhibiting the enzymatic activity of caspase-3 (Tanel and Averill-Bates 2005). Apoptosis occurs at doses ranging from 5 to 25 µM of acrolein. Higher doses might cause cell necrosis. Both α-tocopherol and

ascorbic acid can modulate the apoptotic effects (Nardini et al. 2002).

Acrolein induces a dose-dependent increase in reactive oxygen species from brain mitochondria and decreases glutathione content (Luo and Shi 2005). It can induce mitochondrial stress in brain mitochondria or spinal-cord tissue (Shi et al. 2002; Luo and Shi 2004). Acrolein exposure can lead to time- and dose-dependent reactive oxidant species generation and lipid peroxidation in spinal-cord tissue. Antioxidants can reduce acrolein-induced membrane damage and cell death. All of these studies involved in vitro exposures; their relevance to human in vivo exposures is not known.

REGULATORY SUMMARY

In its evaluation of the carcinogenicity of acrolein, the IARC concluded that there is inadequate evidence for the carcinogenicity of acrolein in humans. The IARC also stated that there is inadequate evidence for the carcinogenicity of acrolein in laboratory animals and concluded that the carcinogenicity of acrolein is therefore not currently classifiable in humans (IARC 1995).

The reference concentration (RfC) for acrolein is 0.02 $\mu g/m^3$ (EPA 2003a), based on a human equivalent concentration lowest observed adverse effect level (LOAEL [HEC]) of 20 $\mu g/m^3$ for nasal lesions in rats exposed for 13 weeks (Feron et al. 1978) and an uncertainty factor of 1000.

A search of the literature and published regulations for North America, Asia, Australia, and Europe did not reveal any exposure standards for acrolein.

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

On-road mobile sources account for approximately 24% of ambient acrolein emissions in urban areas. The oxidation of 1,3-butadiene, a component of mobile-source emissions, is an important source of acrolein emissions. Environmental tobacco smoke is a major source of acrolein indoors. Because of the limited number of studies, the highly reactive nature of acrolein, and the limitations in sampling methods, the available environmental data for acrolein do not appear to be sufficient to allow an assessment of ambient, indoor, or personal exposures. Additional limitations include the number and type of environments sampled, the number of samples collected, the method of accounting for the presence or absence of sources, the extent of geographic and seasonal variability, the representativeness of residences and populations sampled, and the extent of sampling for sensitive or at-risk populations. The available data did suggest, however, that personal mean and peak exposures for adults and children were similar and were lower than 15 $\mu g/m^3$ and that mean personal exposures were two or more times higher than measured ambient or indoor concentrations. Peak personal-exposure concentrations were similar to peak ambient concentrations. The highest peak concentration, at 21 $\mu g/m^3$, was recorded in a residence. The limited data for urban roadside and urban in-vehicle acrolein concentrations suggested that exposures in these environments were considerably lower, both as mean and peak concentrations, than for other outdoor areas, residences, schools, or personal exposures. Measurements from tunnel studies indicated concentrations that were surprisingly low (< 0.6 $\mu g/m^3$), given that on-road mobile sources, again, account for 24% of urban acrolein emissions. Differences in sampling and sample analysis might affect the absolute concentrations reported in the various studies, but it was beyond the scope of this report to assess sampling and sample analysis.

TOXICITY

Acrolein is a reactive, water-soluble compound that is strongly irritating at concentrations of 2 to 4 mg/m^3 in laboratory animals and approximately 2.33 mg/m^3 in humans. Because of these properties, the inhaled compound is not likely to be distributed beyond the nasal cavity and the upper respiratory tract, nor is it likely to be able to reach the DNA of a living cell. In Syrian hamsters exposed for 52 weeks, neither orally administered acrolein nor inhaled acrolein resulted in cancer. Studies in vitro demonstrated that the compound is weakly mutagenic and shows some evidence of binding to biomolecules, particularly those with sulfhydryl groups (proteins containing cysteine, histidine, and lysine). Other studies in vitro indicated that acrolein inhibits cytokine release from macrophages through inhibition of transcription factors and induces apoptosis and generation of reactive oxygen species. The significance of these in vitro findings for expected effects in vivo is limited because of the poor distribution of the inhaled compound due to its high reactivity.

HUMAN HEALTH

Acrolein is a respiratory irritant in humans at relatively low concentrations (700 $\mu g/m^3$). In vitro, acrolein causes inhibition of glutathione, a key antioxidant in the lower respiratory tract. Reductions in glutathione are seen in diseases such as idiopathic pulmonary fibrosis, cystic

fibrosis, and bronchopulmonary dysplasia. When glutathione was administered to patients with idiopathic pulmonary fibrosis, increases in glutathione levels in the epithelial-lining fluid were observed. Reductions in antioxidant protection and scavengers predispose individuals to emphysema, lung inflammation, and fibrosis. The EPA has determined that the potential carcinogenicity of acrolein cannot be determined from the available data (EPA 2003a).

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of acrolein?

Mobile-source emissions account for some (approximately 24%) of the ambient concentrations of acrolein. Other mobile-source emission air toxics (e.g., 1,3-butadiene) might contribute to acrolein concentrations through atmospheric reactions. Shortcomings in the sampling techniques used for these measurements and a paucity of air-sampling data limit confidence in these numbers.

2. Does acrolein affect human health?

Acrolein is a potent respiratory irritant, especially in the upper airway. Because acrolein is a highly reactive, water-soluble molecule, it might not reach other areas of the body in appreciable concentrations.

3. Does acrolein affect human health at environmental concentrations?

Provided that measured ambient concentrations of acrolein (approximately 15 $\mu g/m^3$) are correct, these concentrations are much lower than those that cause irritation in humans (approximately 700 $\mu g/m^3$). However, maximum exposure concentrations indoors are in the same range as those observed to cause irritation in humans.

RESEARCH GAPS AND RECOMMENDATIONS

EXPOSURE

Studies measuring acrolein in urban settings (e.g., near roadways, refineries, incinerators, and where smokers congregate) are limited. Many of these studies use collection systems in which acrolein is unstable, leading to possible underestimation of actual exposures. Research recommendations for acrolein-exposure studies include the following:

- Conduct further research to develop and validate improved exposure monitors for acrolein.
- Collect exposure data on acrolein in urban, suburban, and rural settings as well as in indoor environments and for personal exposures.

TOXICOLOGY

Acrolein is a reactive, irritating compound. Research recommendations for acrolein toxicology studies include the following:

- Further evaluate doses and inflammatory responses to acrolein, particularly in the lower respiratory region in animal studies.
- Conduct additional studies to address the distribution of inhaled acrolein in the respiratory tract and the exposure concentration required to induce inflammation. Of greater concern than the inhalation of the parent compound is the possible formation of acrolein as a metabolite of 1,3-butadiene, a form in which acrolein could be much more widely distributed in the body. For this reason, studies to determine the percentage of inhaled 1,3-butadiene that is metabolized to acrolein should be conducted.

HUMAN HEALTH

There is a striking lack of information about the effects of acrolein on human health. Research recommendations for human-health studies of acrolein include the following:

- Conduct epidemiologic studies if suitable populations can be found.

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