CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of acrolein is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of acrolein.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

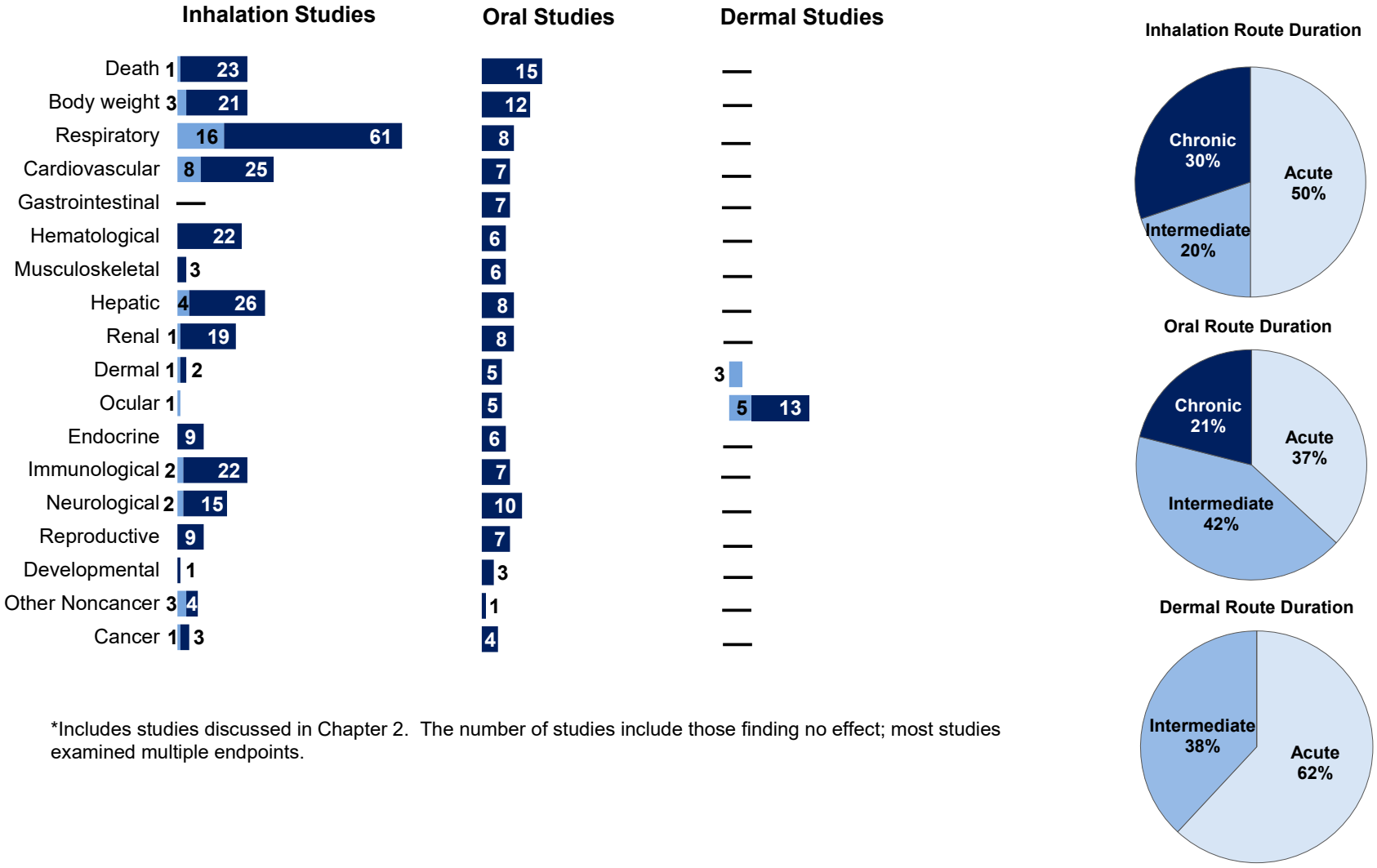
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to acrolein that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of acrolein. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on Acrolein by Route and Endpoint*

Potential respiratory effects was the most studied endpoint
The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; most studies examined multiple endpoints.

Acute-Duration MRLs. An acute-duration inhalation MRL was derived for acrolein. The available acute oral database was inadequate for deriving an MRL. Only one study was available where measured effects were seen in the absence of increased mortality (Conklin et al. 2010). The biological significance of the clinical chemistry changes observed in this study is unclear. Acute-duration oral studies that include histological examination of the gastrointestinal tract may provide data regarding sensitive irritant effects that could serve as a basis for an acute-duration oral MRL.

Intermediate-Duration MRLs. An intermediate-duration inhalation MRL was adopted from the chronic-duration inhalation MRL derived for acrolein. Respiratory effects were observed in animals following intermediate-duration exposure; however, due to limitations in these studies (number of animals studied, number of dose groups, limited respiratory endpoints), these studies were not used for derivation of an MRL (Bouley et al. 1975; Dorman et al. 2008). Additional, more comprehensive intermediate-duration inhalation studies would be useful for derivation of an intermediate-duration inhalation MRL. An intermediate-duration oral MRL was derived for acrolein.

Chronic-Duration MRLs. A chronic-duration inhalation MRL was derived for acrolein. The oral database is inadequate to derive a chronic-duration oral MRL. Chronic-duration oral studies were performed in rats, mice, and dogs; however, extensive histopathological examination revealed no effects in any organs (Parent et al. 1991a, 1992a, 1992b). Reduced survival of mice and rats (a frank effect level) was observed at relatively low doses, although no cause of death could be determined. Additional chronic-duration oral studies are unlikely to identify a NOAEL and/or less serious LOAEL that would be useful for derivation a chronic-duration oral MRL.

Health Effects.

Reproductive. No evidence of reproductive toxicity has been found in animal studies by the oral and inhalation route; however, studies evaluating reproductive function following acrolein inhalation are limited. Additional reproductive toxicity studies by the inhalation route would be useful. Reproductive performance was not affected in 2-generation oral rat studies suggesting that no further oral studies are needed.

Developmental. Only a single study evaluated developmental effects in animals after inhalation exposure to acrolein during pregnancy and limited endpoints were examined (i.e., fetal number and body weight only). Oral prenatal and multigeneration studies suggest that developmental effects of acrolein may be dependent on frank maternal toxicity. Further animal

studies providing information on pre- and postnatal developmental toxicity of acrolein after inhalation and oral exposure would be useful.

Immunotoxicity. Information regarding immunological effects of acrolein in humans is limited to a single controlled exposure study examining cytokine levels in serum and sputum. Additional epidemiology studies evaluating possible associations between immune function and acrolein exposure would be useful. Experimental animal studies of immune function and inflammatory responses following acrolein inhalation have yielded mixed results with immune suppression suggested in some, but not all, cases. Studies using a battery of immunotoxicity tests to correlate exposure concentrations with specific endpoints of immune response would be useful.

Genotoxicity. A limited number of *in vivo* genotoxicity studies have been conducted. Further studies in animals would be useful to determine the ability of acrolein to induce chromosomal aberrations after exposure. Cytogenetic analysis of peripheral lymphocytes of workers exposed to acrolein would provide an opportunity to assess its genotoxicity in humans.

Epidemiology and Human Dosimetry Studies. The human studies database for acrolein is limited to a few controlled-exposure studies using human volunteers and several epidemiological studies evaluating predominantly respiratory and cardiovascular effects associated with biomarkers of acrolein exposure. Due to low confidence in biomarkers of exposure, epidemiology studies correlating the potential health effects with external measures of acrolein exposure would be helpful to determine the nature and severity of currently identified hazards (respiratory, immunological, and gastrointestinal endpoints) as well as other systems with suggestive findings in humans that are too limited to determine hazard potential (e.g., cardiovascular endpoints).

Biomarkers of Exposure and Effect. Available biomarkers of acrolein exposure (urinary metabolites and serum acrolein) and effect (acrolein-adducted DNA, thiols, and lysine) are not capable of distinguishing between exogenous and endogenous acrolein sources. Because acrolein is produced endogenously by a variety of physiological processes (see Section 3.1) including many disease states, it is unclear whether additional research is likely to yield specific biomarkers that are useful for assessing exogenous exposure.

Absorption, Distribution, Metabolism, and Excretion. There are no data in humans on absorption, distribution, metabolism, or elimination of acrolein under controlled exposure circumstances;

however, collection of such data is problematic due to its reactivity and toxicity. Toxicokinetic data are available in animals after inhalation and oral exposure. There are no *in vivo* data on the toxicokinetic behavior of acrolein in animals exposed dermally, and these data would facilitate an understanding of whether there are route-specific differences. The metabolism of acrolein and excretion of urinary metabolites in rats exposed orally and in *in vitro* systems is relatively well understood, but there are few data available to evaluate whether inhalation leads to different metabolic pathways or kinetics.

Comparative Toxicokinetics. No studies were located regarding comparative toxicokinetics of acrolein *in vivo*. Although similar inhalation effects have been observed in rats and humans (Cassee et al. 1996a; Weber-Tschopp et al. 1977) at comparable exposure levels, the animal species that serves as the best model for extrapolating results to humans remains unknown.

Children's Susceptibility. Although no data are available describing age-related differences in acrolein toxicity, acrolein is expected to affect children by the same mechanisms through which it affects adults. However, data are needed to determine if tissue-specific, age-related differences exist for glutathione levels, possibly resulting in an increased sensitivity to acrolein, particularly for respiratory effects. Children with asthma and reactive airway dysfunction may exhibit effects at levels different than adults with similar sensitivities (Annesi-Maesano et al. 2012).

Physical and Chemical Properties. Physical and chemical property data are essential for estimating the partitioning of a chemical in the environment. Physical and chemical property data are available for acrolein and are sufficient for estimating the environmental fate of acrolein (Amoore and Hautala 1983; Daubert and Danner 1987; Gaffney et al. 1987; Hansch and Leo 1995; Lewis 1997; NLM 2024; O'Neil 2013; Seidell 1941; Tomlin 2003; Verschueren 2001).

Production, Import/Export, Use, Release, and Disposal. Data regarding the production methods for acrolein, production facilities, use, and disposal are adequate (Etzkorn et al. 2002). Data regarding current gross estimates of production volumes and capacities are available (EPA 2022a). Production data may be difficult to obtain since many companies desire to maintain their confidentiality. There is limited information regarding import/export of acrolein and reporting is considered CBI (EPA 2022a). Data regarding release of acrolein into air are available for mobile and stationary sources (CEPA 2002; EPA 1998a, 2022h; WHO 2002). Acrolein has been released to the air by the photodegradation of plastic debris and emissions from dairy silages and other feedstuffs (Lomonaco et al. 2020; Malkina et al. 2011). Limited data are available on the release of acrolein to publicly owned treatment works (POTWs) and the

release of acrolein as a pesticide to irrigation waters in California (EPA 1991, 2003), but no data could be located on release of acrolein to soil. Use, release, and disposal information is useful for determining where environmental exposure to acrolein may be high. Determining the percentage of acrolein used as a captive intermediate (i.e., consumed in closed processes in which the compound is not isolated) rather than as an isolated, refined product is important in estimating the amount of release to the environment from stationary, non-combustion-related sources. An estimate of the amount of acrolein released from stationary sources would be useful in establishing the relative importance of each source of acrolein. Even with the availability of information on the production, use, and disposal of acrolein, the amounts released would be difficult to estimate, since major factors contributing to its occurrence in the environment are its formation as a product of the photochemical degradation of other atmospheric pollutants and its release in emissions from a wide variety of combustion processes.

Environmental Fate. The environmental fate of acrolein in air is well studied (Atkinson 1985; Atkinson et al. 1987; Gardner et al. 1987; Grosjean 1990). Given that acrolein occurs in the atmosphere from both natural and anthropogenic sources (DOI 1994; EPA 1998a; Ghilarducci and Tjeerdema 1995; Graedel et al. 1978; Hodgkin et al. 1982; Jonsson et al. 1985; Lipari et al. 1984; Liu et al. 1999a, 1999b; Maldotti et al. 1980; Spada et al. 2008; WHO 1991, 2002), it would be helpful to have estimates of the relative contributions of these sources to acrolein concentrations in air, especially the contribution of the photochemical production of acrolein. Data on the dissipation and degradation of acrolein in water are available (Bowmer and Higgins 1976; Bowmer et al. 1974; EPA 1979; Ghilarducci and Tjeerdema 1995; Kissel et al. 1978; Marron et al. 2020; Nordone et al. 1996a, 1996b; Smith et al. 1995; Tabak et al. 1981; USGS 1998a). No data were located on the removal of acrolein from water through reactions with dissolved and suspended organic matter in water. Studies on this route of removal of acrolein from water would be useful for determining the lifetime of acrolein in waters with high organic content. Measured soil-water partition coefficient data are not available. This information would be helpful for describing the absorption and mobility of acrolein in soil. Experimental data pertaining to the persistence of acrolein in soil and groundwater are lacking. Studies on volatilization from soil surfaces, anaerobic biodegradation in soil and simulated groundwater, and aerobic biodegradation in simulated groundwater would be useful in establishing the likelihood of exposure near hazardous waste disposal sites resulting from volatilization from soil surfaces or from groundwater contamination.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of acrolein from environmental media. Since acrolein has been detected in ambient air and in food and beverages (ppb levels), it is important to determine if acrolein can be absorbed by humans from

environmental samples. However, the chemical structure of acrolein makes it a highly reactive molecule, which presumably is why its effects are, for the most part, restricted to the area of exposure (i.e., respiratory system for inhalation exposure or localized skin damage for dermal exposure). The limited information available regarding inhalation absorption of acrolein in experimental animals demonstrated uptake in respiratory tract tissues, but did not indicate whether systemic distribution occurred (Egle 1972; Morris 1996; Morris et al. 2003). Virtually no information is available regarding absorption by the gastrointestinal tract or skin; additional studies would be useful in establishing whether acrolein is absorbed through these sites or is retained.

Food Chain Bioaccumulation. Measured and estimated BCF values for acrolein indicate that this compound would not bioaccumulate significantly in fish (Bysshe 1982; Hansch and Leo 1995; Veith et al. 1980). No information was available on the bioaccumulation of acrolein in organisms at other trophic levels in aquatic environments. Monitoring for the accumulation of acrolein in organisms from several trophic levels would be useful in estimating the levels of acrolein to which humans are exposed through dietary intake.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of acrolein in contaminated media at hazardous waste sites are needed so that the information obtained on levels of acrolein in the environment can be used in combination with the known body burden of acrolein to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Data are available regarding the detection of acrolein in the environment, most notably in ambient air (Cahill 2014; Destaillats et al. 2002; EPA 2023a; Griffiths et al. 2022; Highsmith and Zweidinger 1988; IARC 2021; Lioy et al. 2011; Logue et al. 2010; Mason et al. 2011; McCarthy et al. 2006; Mohamed et al. 2002; Morello-Frosch et al. 2000; Scheepers et al. 2017; Seaman et al. 2007; Singh et al. 2015; Spada et al. 2008; WHO 1991, 2002), and also in water (de Oliveira Moura et al. 2019; WQP 2023), soil, and sediment (WQP 2023). Additional information on exposure to acrolein in air in urban areas, rural areas, and near hazardous waste disposal sites, as well as in water (specifically, drinking water supplied from groundwater down gradient from hazardous waste disposal sites and contaminated surface waters) and soil at waste disposal sites would be useful. Monitoring air and water over a 1-year period would provide some indication of seasonal variations.

Exposure Levels in Humans. Data for residential exposure to acrolein are limited to a probabilistic study that provided a 24-hour time-weighted estimate of acrolein concentrations in air and inhalation

intake for Canadian residents (Environment Canada 2000) and a study on exposure of nonsmokers in the United States to acrolein in ETS (Nazaroff and Singer 2004). The development of a program for monitoring environmental media would provide information for better estimations of acrolein exposure levels in humans. Data are not available for intake of acrolein through the diet. Market basket surveys or total diet studies similar to those conducted by the U.S. Food and Drug Administration (FDA) are needed to provide data on typical levels of exposure via dietary intake given the presence of acrolein in a number of foods (Casella and Contursi 2004; Feron et al. 1991; Ferreira et al. 2018; Jiang et al. 2022). Monitoring studies of acrolein concentrations in air are available for a few occupations such as shipyard workers, welders, plastic manufacturers, food service employees, and firefighters (Feng et al. 2022b; Fent et al. 2022; Griffiths et al. 2022; Henriks-Eckerman et al. 1990; IARC 2021; Navarro et al. 2021; NIOSH 1982, 1983, 1986; O'Dell et al. 2020; Vainiotalo and Matveinen 1993). Given the high likelihood of occupational exposures to acrolein as a consequence of its emission from combustion sources and the variability in the frequency and amount of exposure to the compound in various occupational settings, additional monitoring data are needed to provide reliable estimates of average daily intake of acrolein in workers.

Exposures of Children. Data on the exposure of children to acrolein are very limited (Nazaroff and Singer 2004; WHO 2002). For children living in a residence where one or more individuals smokes some form of tobacco product, long-term exposure to acrolein and other compounds in ETS are expected (Nazaroff and Singer 2004; WHO 1999). Lifetime exposures to acrolein in ETS have been estimated for individuals residing with one or more smokers (Nazaroff and Singer 2004); however, there are no data that specifically address the inhalation intake of acrolein from ETS in individuals below the age of 18 years. Information on acrolein concentrations in indoor air is limited for residences in the United States (Highsmith and Zweidinger 1988; Seaman et al. 2007). More data are needed to adequately assess the exposures of children to acrolein generated from indoor combustion sources, especially tobacco and other smoking products. Determination of the average daily intake of acrolein would be complicated by the variability in the frequency and amount of exposure to cigarette smoke and other acrolein sources. Therefore, exposure studies should be structured to assess the temporal variations in acrolein concentrations over a typical day and should also account for seasonal changes in air exchange within a residence (i.e., winter versus summer). It may be possible to use data obtained from NHANES for age-related exposure by controlling for smoking-related exposure. For children who are not exposed to ETS in the home environment, it is expected that the largest exposure to acrolein will be through inhalation of ambient air, especially in urban areas, and through the diet. Therefore, studies that are tailored to assessing exposure of children to acrolein in ambient air would be useful given the tendency for some

children to spend more time outdoors than many adults. Also, market basket surveys or total diet studies similar to those conducted by the FDA would be useful for providing data on typical levels of exposure via dietary intake for children.

6.3 ONGOING STUDIES

There are several ongoing studies evaluating the potential adverse effects of acrolein exposure in humans and laboratory animals as well as studies of mechanisms of toxicity (Table 6-1).

Table 6-1. Ongoing Studies on Acrolein

Investigator	Affiliation	Research description	Sponsor
Human studies			
Benowitz, Neal	University of California, San Francisco	Biomarkers of cardiovascular risk and exposure to non-nicotine toxicants in electronic cigarette users	NIDA
Bhatnagar, Aruni	University of Louisville	Cross-sectional study of VOC exposure with cardiometabolic disease	NIEHS
Gabuzda, Dana	Dana-Farber Cancer Institute	Assessment of longitudinal clinical samples for markers of inflammation, vascular injury, and oxidative stress in marijuana users	NIDA
Hatsukami, Dorothy	University of Minnesota	Evaluation of tobacco biomarkers (acrolein metabolites) in biological samples	NCI
Haynes, Erin	University of Kentucky	Intervention study evaluating the impacts of mitigation efforts on outdoor and indoor air concentrations of acrolein and their association with stress and quality of life metrics	NIEHS
Hecht, Stephen	University of Minnesota	Clinical study evaluating markers of exposure (urinary levels of acrolein metabolites), markers of effect (DNA damage and epigenetic changes), and cancer risk in former smokers and never smokers	NCI
Johnson, Natalie	Texas A&M University	Air sampling of acrolein and monitoring of symptoms among residents of East Palestine, Ohio	NIEHS
Murphy, Sharon	Wake Forest University	Cohort study of e-cigarette exposure and markers of inflammation and oxidative stress	NCI
Whitlow, Chrispher	Wake Forest University	Longitudinal study evaluating vaping exposure on adolescent brain function and behavior	NCI
Woo, Daniel	University of Cincinnati	Case-control study of polyamine and acrolein exposure and cerebral small vessel disease	NINDS
Animal and mechanistic studies			
Conklin, Daniel	University of Louisville	Cardiovascular and pulmonary toxicity of electronic nicotine delivery systems (ENDS) in animal models	NHLBI
Hecht, Stephen	University of Minnesota	Acrolein metabolism and excretion with co-administration of watercress (source of 2-phenethyl isothiocyanate)	NCI

Table 6-1. Ongoing Studies on Acrolein

Investigator	Affiliation	Research description	Sponsor
Khasawneh, Fadi	Texas A&M University	Role of third-hand smoke (THS) constituents, including acrolein, in platelet-dependent diseases	NHLBI
Kimura, Shioko	NCI	Role of secretoglobin (SCGB) 3A2 in protecting lung cells from cigarette smoke constituents, including acrolein	NCI
Leikauf, George Douglas	University of Cincinnati	Pathophysiological mechanisms of acrolein-induced acute lung injury in mice	NIEHS
Mohan, Rajiv Ravindra	Harry S. Truman Memorial VA Hospital	Evaluation of ocular injuries following acute and chronic exposure to acrolein and development of mitigating topical treatments	Veterans Affairs
Srivastava, Sanjay	University of Louisville	Mechanisms (role of MiR-21) of macrophage activation in atherosclerosis from exposure to acrolein in electronic nicotine delivery systems	NHLBI

DNA = deoxyribonucleic acid; NCI = National Cancer Institute; NHLBI = National Heart, Lung, and Blood Institute; NIDA = National Institute on Drug Abuse; NIEHS = National Institute of Environmental Health Sciences; NINDS = National Institute of Neurological Disorders and Stroke; VOC = volatile organic compound

Source: National Institute of Health (NIH) RePORTER 2024