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Environmental Aldehyde Sources and the Health Implications of Exposure

Pritam Sinharoy, Stacy L. McAllister, Megana Vasu, and Eric R. Gross

Abstract Aldehydes, which are present within the air as well as food and beverage sources, are highly reactive molecules that can be cytotoxic, mutagenic, and carcinogenic. To prevent harm from reactive aldehyde exposure, the enzyme aldehyde dehydrogenase 2 (ALDH2) metabolizes reactive aldehydes to a less toxic form. However, the genetic variant of ALDH2, ALDH2*2, significantly reduces the ability to metabolize reactive aldehydes in humans. Therefore, frequent environmental aldehyde exposure, coupled with inefficient aldehyde metabolism, could potentially lead to an increased health risk for diseases such as cancer or cardiovascular disease.

   Here, we discuss the environmental sources of reactive aldehydes and the potential health implications particularly for those with an ALDH2*2 genetic variant. We also suggest when considering the ALDH2*2 genetic variant the safety limits of reactive aldehyde exposure may have to be reevaluated. Moreover, the ALDH2*2 genetic variant can also be used as an example for how to implement precision medicine in the field of environmental health sciences.

Keywords Reactive aldehyde · Aldehyde dehydrogenase 2 · Cigarette · Alcohol · 4-HNE · ALDH2*2

1   Introduction

Aldehydes are highly reactive electrophiles abundant within our environment. Many sources of aldehydes exist and are present within the air we inhale in addition to the products we use and consume. Exposure to these aldehydes occurs outdoors and indoors, including within the workplace. Lifestyle choices such as tobacco cigarettes, e-cigarettes, and alcohol also expose people to aldehydes. Aldehydes are also present in foods, nonalcoholic beverages, cosmetics, and hand sanitizers (Fig. 1).

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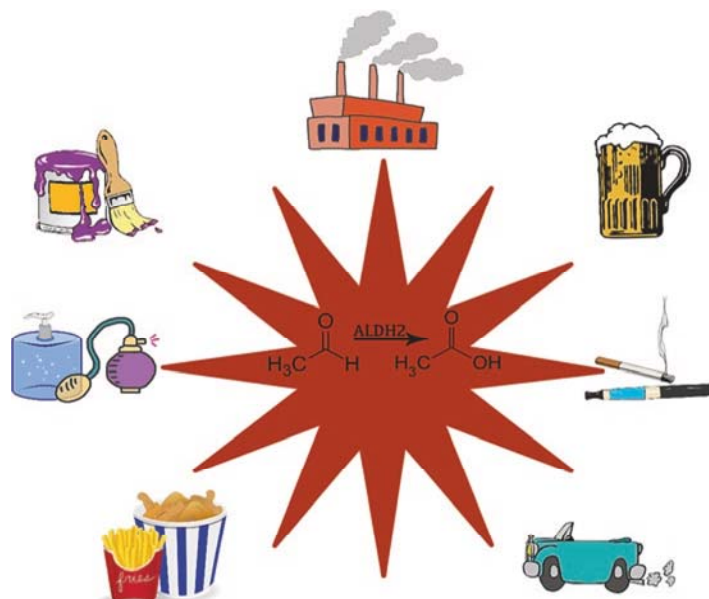e-mail: ergross@stanford.edu

Fig. 1 Exogenous sources of reactive aldehyde exposure. These include air pollution produced by industrial power plants and automobiles, alcoholic beverages, tobacco products including cigarettes and e-cigarettes, fried foods, cosmetics, and lacquers in paints. As pictured, the ALDH2 enzyme reduces an aldehyde to a less harmful acid. However, for those with an ALDH2*2 variant, the efficiency of this metabolism is reduced by >60%

Together, exposure to these aldehyde sources, coupled with genetic differences which reduce aldehyde metabolism, may influence the risk of developing diseases such as cancer and cardiovascular disease.

Environmental aldehyde sources include those such as acrolein, acetaldehyde, and formaldehyde. Acrolein is considered a human carcinogen that irritates the upper respiratory tract when inhaled. Acetaldehyde and formaldehyde are also classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC) [1]. These toxic properties of aldehydes are due to their electrophilic nature, which can modify DNA and proteins, thus the label "reactive" aldehydes [2, 3]. For example, acrolein reacts with proteins specifically on histidine, cysteine, and lysine amino acids by Michael addition or Schiff base formation [4]. Acrolein can also block protein sulfhydryl group formation on lysine residues and result in impaired protein function [5]. Overall, these effects from exogenous sources of reactive aldehydes can be cytotoxic, mutagenic, and carcinogenic.

A critical enzyme responsible for reducing aldehydes to less reactive forms is aldehyde dehydrogenase 2 (ALDH2). ALDH2, primarily known for metabolizing acetaldehyde (produced as an intermediate in the metabolism of alcohol to acetic acid), is also important in the detoxification of other reactive aldehydes such as formaldehyde and acrolein [6, 7]. However, individuals with an ALDH2 genetic variant have significantly reduced enzymatic activity to metabolize these aldehydes.

In homozygotes for the ALDH2 variant (ALDH2*2/*2), the metabolism of aldehydes is severely limited (~96% activity loss), whereas in heterozygotes (ALDH2*1/*2) the enzymatic activity is reduced by 60–80% relative to those individuals that are without the variant (ALDH2*1/*1) [2, 8]. Throughout this rest of this chapter, we will denote the ALDH2 variant as ALDH2*2.

With exposure, the limited ability to metabolize reactive aldehydes for those with the ALDH2*2 variant can potentially pose an increased risk for developing diseases such as cancer or cardiovascular disease. However, some of these environmental exposures could be easily modifiable. Here we discuss the sources of reactive aldehydes within the environment and their effects on human health, particularly for those with a limited ability to metabolize reactive aldehydes.

2 Outdoor, Indoor, and Occupational Aldehyde Exposure

In this section, we will discuss the outdoor, indoor, and occupational exposure of reactive aldehydes and how these exposures may potentially impact people with an ALDH2*2 genetic variant. These exposures include air pollution from automobiles and industrial waste, indoor sources such as paint, and occupational sources such as working with aldehydes and surgical smoke.

2.1 Outdoor Exposures

2.1.1 Air Pollution

Air pollution is a significant concern for Asian countries but also a concern for the United States. According to the World Health Organization (WHO), air pollution is the greatest environmental risk to human health [9]. Sources of air pollution can be natural or anthropogenic and include biomass and fossil fuel combustion, automobile exhaust, and industrial power plant and wood burning fumes [10–12]. Typical city or urban air pollutant exposure consists of aldehydes, ketones, hydrocarbons, and particulate matter. The studies below detail how aldehydes contribute to air pollution.

At six locations in Japan including in urban cities (Sanda, Nishiwaki, Toyooka, and Sumoto), at roadside (Ashiya), and at an industrial site (Takasago), researchers measured 101 volatile organic compound (VOC) concentrations, including acetaldehyde and formaldehyde [13]. Relative to carcinogenic effect, hazardousness of these compounds was evaluated by calculating the factor called excess cancer incidence. For formaldehyde at all sites, the excess cancer incidence exceeded 10^{-5} per $\mu g\ m^{-3}$. This is a level of concern for a carcinogenic effect since the United States Environmental Protection Agency quantitatively estimates that there is a carcinogenic risk for formaldehyde at or above 1.3×10^{-5} per $\mu g\ m^{-3}$ [13]. The authors

concluded that elevated VOCs, such as formaldehyde, were partially attributed to higher traffic levels generating greater amounts of automobile exhaust in the designated areas [12, 13]. Overall, these studies emphasized the potential harm one exogenous source of pollution, automobile exhaust, can potentially have on changing the risk for carcinogenesis.

In Asia, ambient carbonyl compound concentrations were assessed in seven major cities (Beijing, Chengdu, Guangzhou, Shanghai, Wuhan, Xiamen, and Yantai) and two rural areas (Qinghai Lake, Qinghai, and Lhasa, Tibet) during both the summer and winter seasons. These average concentrations showed seasonal variability dependent on temperature. Among the nine sampling sites measured, the average concentrations of propionaldehyde, formaldehyde, and acetaldehyde were found to be 0.25, 5.07, and 1.91 ppb by volume in the summer and 0.17, 2.04, and 1.42 ppb by volume during the winter, respectively [14]. This study also found the relatively high levels of acetaldehyde emissions were a direct result of increased use of ethanol-blended gasoline (e-gasoline) in vehicles during the summer season.

In Beijing, ambient air aldehyde contents were also measured, and the concentrations of formaldehyde, acetaldehyde, and acrolein were found to be 29.3 ± 15.1 μg/m^3, 27.1 ± 15.7 μg/m^3, and 2.3 ± 1.0 μg/m^3. These levels are considered at the high end of concentration ranges measured in cities around the world [15]. For example, in Savannah, Georgia, the relative levels of formaldehyde and acetaldehyde were 2.0 μg/m^3 and 2.3 μg/m^3, compared to Beijing concentrations of 29.3 ± 15.1 μg/m^3 and 27.1 ± 15.7 μg/m^3, ~14 times lower than that of Beijing [16].

Air pollution-mediated aldehyde exposure is highly concerning for those with an ALDH2*2 variant especially living in major East Asian cities. Air pollution continues to be a significant source of environmental reactive aldehyde exposure throughout East Asia and in particular China. Therefore, the overall risk for exposure for individuals with an ALDH2*2 variant, particularly with the increased migration to urban cities, is of potential concern. Below, we will discuss in more detail automobile exhaust and industrial waste which also contribute to outdoor levels of reactive aldehydes.

2.1.2 Automobiles

Automobile exhaust includes the reactive aldehydes formaldehyde, acetaldehyde, and acrolein [26]. These aldehydes are produced during the burning of fossil fuels and constitute ~1–2% of the volatile organic compounds produced from vehicle exhaust [13]. In one study, diesel engine exhaust gas emission was monitored using three types of diesel fuel (red diesel, biofuel, and gas oil). In all types of diesel fuel, the most abundant reactive aldehydes were formaldehyde, acetaldehyde, and acrolein that were all within a range of 1000–2000 ppb [17]. Biofuel diesel had the greatest levels of acetaldehyde when compared to red diesel and gas oil.

With their increasing popularity, reformulated automotive fuels are an additional source of aldehyde emission. Depending on whether ethanol or methanol is added to the automotive fuels, an increased amount of acetaldehyde or formaldehyde is

emitted in automobile exhaust. In a study comparing ethanol-blended fuel exhaust with gasoline exhaust, ethanol-blended exhaust emits predominantly acetaldehyde (1.2–12 g/kWh), whereas gasoline exhaust emits predominantly formaldehyde (0.74–2.3 g/kWh) [18]. With increased ethanol blending, acetaldehyde emissions increased so that pure ethanol used as fuel had acetaldehyde emissions 35–44 times higher than gasoline. Ethanol also influenced formaldehyde emissions so that addition of 50% ethanol to gasoline resulted in a 30–50% increase in formaldehyde emissions [18].

The increased popularity of gasoline-electric, hybrid cars and electric cars facilitates a reduction in automobile emission of acetaldehyde and formaldehyde that may potentially assist in alleviating the elevated levels measured in major cities described above. For ALDH2*2 variant, vehicle selection could also potentially reduce direct reactive aldehyde exposure while driving an automobile.

2.1.3 Industrial Waste

During industrial manufacturing, aldehydes are released as a by-product into the atmosphere. Significant sources of reactive aldehydes produced during the manufacturing process include formaldehyde, butyraldehyde, acetaldehyde, and acrolein. Formaldehyde and butyraldehyde are used as precursors for resin and plasticizer (softener) production, respectively [19]. The reactivity and availability of butyraldehyde makes it a popular material in plasticizer production and other industrial materials [20]. Formaldehyde is used extensively in commercial processes such as in the synthetic resin industry, due to its high chemical reactivity and thermal stability. In Hong Kong, an industrial workplace pilot study found formaldehyde as the most abundant carbonyl compound among all workplace air samples, accounting for 22.0–44.0% of total carbonyls measured on a molar basis. When formaldehyde levels were measured in a paint and wax manufacturing plant and a food-processing factory, formaldehyde levels exceeded the WHO air quality guideline of 81.8 ppb [20].

During the manufacturing processes, combustion emissions are of optimal importance. Combustion sources include power plant petrochemical, diesel-fueled engines, and polyethylene plastic, which release formaldehyde, acetaldehyde, and acrolein [21, 22]. Manufacturing-based acrolein emissions also include volatilization from treated waters and contaminated waste streams, formation as a photooxidation product of various hydrocarbon pollutants, and use in petroleum operations [23–25].

Industrial waste carbonyl contents should be closely monitored particularly in East Asian countries where there is a high prevalence of people with the ALDH2*2 variant. Most standards in regard to what is considered a safe level of industrial product exposure are based upon the ability to efficiently metabolize by-products from industrial manufacturing such as aldehydes to less toxic forms. Therefore, reconsidering the standards for what are the safe levels of exposure for these aldehydes in the industrial workplace or from industrial waste may need to be considered for those who have an ALDH2*2 genetic variant.

2.2 Indoor Exposures

Within a building, aldehydes can infiltrate from external sources described above or can also be present in the air as a result of generation indoors. In six different New Jersey housing sites, levels of indoor formaldehyde, acetaldehyde, and seven other aldehydes were measured. The combined concentration of these nine aldehydes measured indoors was 63 ± 22 ppb compared to outdoor measured values of 19 ± 11 ppb. Of the nine aldehydes assessed, formaldehyde was the most abundant at 55 ppb with acetaldehyde the second most abundant at 3 ppb [26].

In newly installed and painted buildings, higher acetaldehyde levels were found indoors relative to outdoors, suggesting paint and/or lacquers are a significant acetaldehyde source which declines with building age [27]. Dry lacquers which contain aldehydes such as propanol, n-nonanal, and n-hexanal are also used to paint radiators [28]. This is concerning because after a radiator is painted, the heat generated during radiator use causes dry lacquer combustion and aldehydes to be aerosolized into the air. Other lesser-known indoor aldehyde sources include wood burning fireplaces, gas stoves, gas heaters, and synthetic carpets, which can emit formaldehyde and acrolein [11, 26].

2.3 Occupational Exposure

Persons working in aldehyde production industries or as laboratory technicians, healthcare professionals, or funeral home employees may be exposed to higher levels of aldehydes, especially when working with formaldehyde, acrolein, and acetaldehyde [29, 30].

Occupational exposure to these reactive aldehydes may occur via inhalation of reactive aldehyde vapor or direct skin exposure. For people working directly with formaldehyde in an industrial setting, it was found that ~3.5% of workers were exposed to formaldehyde air concentrations greater than 3 ppm, well above the workplace formaldehyde exposure limit set by OSHA at ~0.75 ppm over an 8-hour workday. In this same study, less than 12% of workers were exposed to concentrations greater than 1 ppm; however, over 88% of workers were exposed to concentrations of 0.5 ppm or higher, nearing the OSHA limit [31].

For healthcare professionals, additional sources of reactive aldehyde exposure include electrocautery smoke and widely used hospital sanitizers and disinfectants. During surgery, electrocautery surgical smoke contains formaldehyde, acetone, benzene, and acrylamide [32]. Hospital disinfectants also contain reactive aldehyde sources including formaldehyde and ortho-phthalaldehyde (OPA) [33]. Laboratory researchers can also be exposed to high levels of aldehydes. For example, in a cancer research institute study, formaldehyde exposure levels for laboratory workers ranged from 4.9 to 268.7 $\mu g/m^3$ [29].

In humans, evidence suggests when using liver mitochondrial fractions that formaldehyde metabolism is ~3× slower for those with an ALDH2*2 variant compared to those that do not [34]. This suggests that exposure to formaldehyde could perhaps be more toxic and potentially carcinogenic for those with an ALDH2*2 variant since formaldehyde cannot be metabolized as efficiently to the less reactive formic acid. Further, exposure of ALDH2 knockout mice to 500 ppm of inhalational acetaldehyde leads to higher erosion and degeneration of the respiratory epithelium (55.6% vs. 22.2%) and dorsal skin (77.8% vs. 0.0%) and hemorrhaging of the nasal cavity for the ALDH2 knockout mice when compared to the wild-type ALDH2 mice [35]. This suggests that workers with the ALDH2*2 variant are potentially more susceptible to harm from inhalational exposure to reactive aldehydes in the workplace. Therefore, standard limits in regard to workplace exposure may have to be re-examined with the ALDH2*2 genetic variant in mind.

Overall, these studies suggest that outdoor, indoor, and occupational sources of reactive aldehydes are prevalent and of potential concern. Elevated exposure to these aldehyde sources could pose an environmental risk for human health especially for those with an ALDH2*2 variant, and the thresholds considered safe for exposure in these environments need to be potentially re-examined.

3 Lifestyle Choices

Lifestyle choices contribute to an increased risk of aldehyde exposure including drinking alcohol, smoking tobacco products, consuming certain dietary sources, and using particular cosmetic products including perfumes. Here, we will discuss specific lifestyle choices that are sources of aldehyde exposure and their implication on human health, especially in the context of people with an ALDH2*2 variant who cannot catabolize aldehydes efficiently.

3.1 Alcohol

A well-known source of reactive aldehyde exposure is alcohol. Upon ingestion, alcohol is converted to acetaldehyde by the enzyme alcohol dehydrogenase (ADH). Acetaldehyde is then metabolized by ALDH2 to the less reactive acetic acid. Within the cell, ALDH2 has the highest enzymatic affinity for acetaldehyde [36, 37]. The biochemical effect of acetaldehyde after alcohol consumption, which includes DNA- and protein-induced adduct formation, has been detailed in recent reviews [38, 39].

Individuals who are heterozygotes for the ALDH2*2 variant result in an accumulation of acetaldehyde which is ~5-fold higher compared to the wild-type ALDH2 enzyme after alcohol consumption [40]. This acetaldehyde accumulation produces the phenotype of facial flushing and elevated heart rate seen in those with an

ALDH2*2 variant. Those homozygous for the ALDH2*2 variant have an aversion to alcohol consumption since the ability to metabolize acetaldehyde is <4% compared to the wild-type ALDH2 enzyme. Thus, the ALDH2*2 variant is considered protective from developing alcoholism, supported since the occurrence of alcoholism is reduced for those individuals with an ALDH2*2 variant [41].

Although the ALDH2*2 variant may protect from alcoholism, individuals who are heterozygotes for the ALDH2*2 variant, ~560 million people worldwide, still consume alcohol. For example, in Korea, where ~20% of the population carries an ALDH2*2 variant, alcohol consumption is one of the highest per capita in the world [42].

In particular, the reduced metabolism of acetaldehyde resulting from an ALDH2*2 variant after alcohol consumption is linked to a risk for developing esophageal cancer and cardiovascular disease. In regard to esophageal cancer, a seminal study by Yokoyama was the first to link an increased incidence of esophageal cancer caused by alcohol consumption to those with an ALDH2*2 genetic variant [43]. The odds of developing esophageal cancer are also dose-dependently related to the amount of alcohol consumed. Even a moderate consumption of alcohol (9–17.9 units/week) for those with an ALDH2*2 variant increases the odds ratio to 40 for esophageal cancer [43, 44]. The importance of relaying this significant health risk to the public in addition to healthcare professionals is critical and is stressed in several studies [45, 46]. Further, the impact of the ALDH2 enzyme on aldehyde metabolism and alcohol-induced cardiomyopathy was recently reviewed [47].

3.2 Cigarettes and E-cigarettes

Smoking imposes a tremendous economic burden accounting for more than $170 billion each year in healthcare costs for adults in the United States and more than $422 billion each year worldwide [48, 49]. To date, smoking remains the leading cause of preventable death in the United States, accounting for one out of five deaths annually [50, 51]. The typical components of a tobacco cigarette are filters (designed to trap smoke), tipping paper (which wraps around the filter), tobacco fillers, cigarette paper (for holding the tobacco fillers), and adhesives. In contrast to cigarettes, the primary components of an e-cigarette are an e-liquid cartridge, an atomizer/heating element, a microprocessor, and a battery (Fig. 2). This is important to note since even though the structural compositions of cigarettes and e-cigarettes are quite different, both of these ways designed to deliver nicotine produce reactive aldehydes.

The smoke from a cigarette is composed of more than 4700 different chemical compounds. These include aldehydes such as formaldehyde, propionaldehyde, butyraldehyde, acetaldehyde, acrolein, and crotonaldehyde [52, 53]. When compared to non-smokers, a person smoking one cigarette produces a 3.5-fold increase in aldehyde levels in the saliva. After smoking ten cigarettes or more a day, a two-fold increase in these compounds was found in the saliva [54]. As these compounds when smoking are inhaled into the lungs, exhaled breath condensate of cigarette

Fig. 2 Schematic illustration describing cigarette and e-cigarette components. Although both are largely different in regard to appearance and the materials used for composition, both cigarette and e-cigarette aerosol contain reactive aldehydes
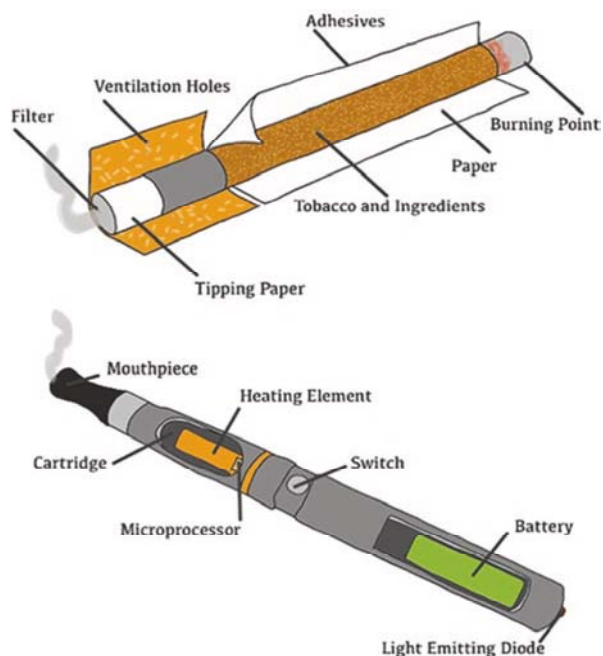
smokers also contains higher levels of endogenous aldehydes including malondialdehyde (57 ± 2 nmol/L), hexanal (64 ± 4 nmol/L), and heptanal (27 ± 4 nmol/L) compared to non-smokers (18 ± 6 nmol/L, 14 ± 4 nmol/L, and 19 ± 1 nmol/L, respectively) [54].

Epidemiological evidence also suggests that smoking is a key factor in developing cancer and cardiopulmonary disease [55]. Particularly reactive aldehydes in cigarette smoke, especially acetaldehyde and acrolein, are directly linked to a higher risk for developing lung, oral, and gastrointestinal cancer [38]. Moreover, aldehyde levels in cigarette and e-cigarette smoke are responsible for 33% of deaths from cardiovascular diseases and 20% of deaths from ischemic heart disease [51]. Aldehydes derived from cigarette smoke affect heart contractile function and damage blood vessel structure and function by affecting vascular endothelial and epithelial cells [56].

Further in regard to the ALDH2*2 variant, a study consisting of 410 Japanese patients who underwent coronary angiography between 2010 and 2016 demonstrated that smokers had a significantly higher prevalence of coronary spastic angina (CSA) (63.1% vs. 48.9%) than non-smokers [57]. Patients with the ALDH2*2 variant also had a higher risk for CSA when compared to non-smokers with a wild-type ALDH2 enzyme (58.5% vs. 40.8%), whereas the ALDH2*2 variant exaggerated the risk in smokers (82.5% vs. 56.6%) when compared to wild-type ALDH2.

Cigarette smoke exposure is also the primary risk factor for chronic obstructive pulmonary disease (COPD) with a general underlying hypothesis that reactive oxygen and reactive aldehydes contribute to the development of COPD [54, 58]. A

recent study including 967 Japanese individuals revealed that the presence of an ALDH2*2 variant was not associated with the development of COPD but having an ALDH2*2 variant was associated with significantly lower lung functioning parameters when compared to individuals with wild-type ALDH2 [59]. Moreover, this study found that 16 weeks of cigarette smoke exposure increased the lung volume and resulted in mild emphysema for wild-type ALDH2 mice, whereas ALDH2*2 variant mice were resistant to emphysema development in response to cigarette smoke exposure. Although the link between cigarette smoking and COPD is clearly established, these data suggest how differences in the metabolism of reactive aldehydes may affect COPD requires further study.

E-cigarette aerosol, similar to cigarettes, also contains reactive aldehydes including acrolein, acetaldehyde, and formaldehyde [60–62]. Moreover, a recent report suggests that when measuring reactive aldehyde content across 66 different e-cigarette liquids, acetaldehyde concentrations are generally ~2 fold higher than formaldehyde or acrolein [63]. However, the quantity of these three reactive aldehydes produced is variable and dependent upon the battery voltage, type of e-cigarette vaporizer, and amount and type of liquid within the e-cigarette cartridge. For example, changing the battery voltage from 3.7 to 4.8 V increases the combined reactive aldehyde production of acetaldehyde, formaldehyde, and acrolein by 3.5-fold. Additionally, a double-coil vaporizer when compared to a single-coil vaporizer will decrease resistance and increase the power. Therefore, higher-power e-cigarettes (9.1 W) can increase acetaldehyde levels ~65-fold, formaldehyde levels ~49-fold, and acrolein levels ~3-fold in the e-cigarette aerosol when compared to a lower-power e-cigarette (4.6 W) [60]. Clearly, e-cigarette research is a new and emerging field, and how e-cigarette aldehyde exposure in combination with genetic differences in reactive aldehyde metabolism may affect the risk of developing diseases such as cardiovascular disease or cancer is largely unknown.

3.3 Beverage and Food Sources

Aldehydes are abundantly found in several dietary sources. Besides alcoholic beverages, methanol and ethanol are natural constituents of fruit juice, which are enzymatically metabolized by the enzyme alcohol dehydrogenase (ADH) into formaldehyde (range from 3.7 to 60 ppm) and acetaldehyde (ranging from 0.0005 to 230 ppm), respectively [64, 65]. Aldehydes are natural components of fruits, vegetables, spices, and nuts. For example, peas contain traces of acetaldehyde, whereas cinnamon contains cinnamaldehyde. Almonds and cherries contain benzaldehyde, whereas anisaldehyde and salicylaldehyde appear in anise and vanilla extracts [66]. Moreover, fermentation is a widely known process used for millennia for preserving food and beverages. According to the WHO, fermented and processed foods including cheese, yogurt, meat, kefir, kimchi, and tofu also contain traceable amounts of formaldehyde (5.7–20 ppm) and acetaldehyde (0.2–0.6 ppm) [64].

Fats are also a significant source of aldehydes, and when cooked, over 20 different aldehydes are produced [66]. Aldehydes are formed when frying food or heating oils to cook food. These aldehydes are mainly generated from the thermal oxidation of the polyunsaturated triacylglycerols [67]. Cooking oil heated at a temperature of 180 °C produces high amounts of aerosolized acrolein (canola oil 53.5 ± 3.9 mg/h and safflower oil 57.3 ± 6.7 mg/h) which are typically inhaled while standing over cooking food [68]. When soybean oil is used to cook deep-fried potatoes, 4-hydroxynonenal (4-HNE) is a major polar lipophilic compound in the thermally oxidized frying oil [69]. Additional studies further validate that deep-frying food, especially at high temperatures and for prolonged periods of time, generate reactive aldehydes [70, 71]. For example, in Taiwan restaurant exhaust streams, 18 carbonyl species were measured. Formaldehyde, acetaldehyde, acetone, and butyraldehyde contributed 55.01–94.52% of total carbonyls in the dining areas for the restaurants measured [72].

3.4 Cosmetics

Cosmetic products including perfumes, deodorants, skin care products, and nail polish removers are common in daily lifestyle. According to the American Cancer Society, professional hair treatment products such as keratin smoothening products contain formaldehyde or formaldehyde-releasing agents which can raise indoor formaldehyde concentrations to a hazardous level (range 0.33–1.88 ppm) in hair salons [73]. Various other aldehydes found in perfumes and deodorants are the most common cause of hypersensitivity to fragrances and allergic reactions [74]. For example, cinnamaldehyde, a well-known chemical irritant and sensitizing agent, is a major component of the "fragrance mix" and commonly found in deodorants [75]. In 1991, when the EPA tested 31 fragrance products, among the 20 most commonly found toxic chemicals were propylene glycol, acetone, benzaldehyde, ethanol, and benzyl alcohol.

Aldehydes are also present in hand sanitizers where a hand sanitizer may contain 60–90% ethanol. During topical application of ethanol and aldehydes, the skin is the most susceptible organ to ethanol- and aldehyde-induced damage. Both ethanol and aldehydes are highly diffusible through the lipophilic layer of the outer skin and can covalently modify the epidermis to form an immunogenic antigen. The antigen-carrying cell can migrate to the lymph nodes, where the antigen is recognized by specific T cells that can proliferate and disseminate throughout the body via the blood, causing an inflammatory skin response [76]. Although there is a lack of evidence linking topical ethanol application to skin cancer, several studies confirm that when taken orally, ethanol increases the risk for skin cancer and other types of cancer [77]. Lastly, considering the susceptible nature of ALDH2*2 variant to ethanol and subsequently generated acetaldehyde-induced health disorders, it is advisable to avoid usage of ethanol-based cosmetic products.

Taken together, these studies suggest alcohol intake, use of tobacco products, fried foods, and cosmetic products are sources of reactive aldehydes. Reactive aldehyde exposure associated with these lifestyle choices increases the chances of developing cancer and cardiovascular diseases [51] specifically for those with an ALDH2*2 variant [78].

4 Impact on Humans with Reduced Reactive Aldehyde Metabolism

Reactive aldehyde exposure damages the electron transport chain, leading to an overproduction of mitochondrial reactive oxygen species (Fig. 3). This in turn affects cellular properties contributing to various diseases [79]. The health implications of reactive aldehyde exposure from these environmental sources listed above are even more concerning for those ~560 million people worldwide who cannot efficiently metabolize these reactive aldehydes due to ALDH2*2 genetic variant. Therefore, people with an ALDH2*2 variant are vulnerable to reactive aldehyde exposure-induced oxidative stress and associated pathophysiological conditions.

Extensive research over the past several years has recognized the ALDH2*2 variant as a major contributor to several human diseases including cardiovascular disorders, stroke, and cancer [2, 38, 80]. For example, a recent meta-analysis of nine case-control studies concluded that the ALDH2*2 variant is associated with an increased risk for developing coronary heart diseases, including myocardial infarction [81]. Therefore, those with an ALDH2*2 variant exposed to exogenous reactive aldehyde sources as discussed above are more likely to develop medical complications as a result of limited reactive aldehyde metabolism.

Since ALDH2*2 individuals are more susceptible to reactive aldehyde-associated health complications, it is important that information regarding the health risks associated with reactive aldehyde exposure be disseminated widely to the public. Many exogenous reactive aldehyde sources, such as alcohol consumption or cigarette use, are avoidable or modifiable. In situations where exposure cannot be avoided, safety precautions can be taken to limit or minimize exposure.

5 Conclusion

Over the past several years, extensive research has advanced the understanding of the relationship between exogenous reactive aldehyde sources and the harmful effects of their exposure. Whether outdoors, indoors, or at the place of occupational employment, the potential for reactive aldehyde exposure and the resultant negative health consequences are particularly important to consider for those with an ALDH2*2 variant.
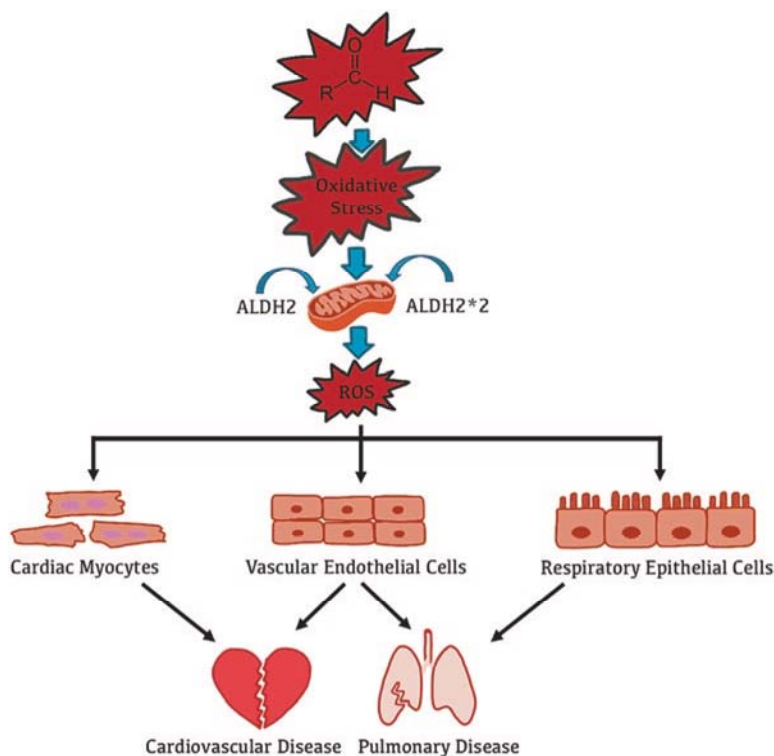
Fig. 3 Schematic representation of how reactive aldehyde exposure harms the cardiopulmonary system. ALDH2 metabolizes toxic reactive aldehydes into a less toxic form. For those with an ALDH2*2 variant, exposure to exogenous reactive aldehydes increases intracellular oxidative stress and impairs mitochondrial function due to an inefficient metabolism of reactive aldehydes. This is followed by an increase in mitochondrial reactive oxygen species (ROS) production. ROS directly affects the structure and function of cardiac myocytes, vascular endothelial cells, and pulmonary epithelial cells, resulting in cellular dysfunction that can ultimately lead to cardiopulmonary disease

At the forefront of protection from environmental sources of reactive aldehydes is public awareness. Unless knowledge is properly disseminated, individuals will not be cognizant of the risks associated with reactive aldehyde exposure or capable of taking the necessary steps to minimize exposure. Precautionary measures and lifestyle modifications to reduce reactive aldehyde exposure should be a focus of public health to ultimately reduce the potential risk for developing cancer or cardiovascular disease.

There are also several key questions that remain unanswered. More research is needed to understand how susceptible those with an ALDH2*2 variant are to reactive aldehydes from environmental sources. In addition, it is also important to further understand how much the relative risk for cancer or cardiovascular disease is increased with reactive aldehyde exposure for those with an ALDH2*2 genetic vari-

ant. Basic and clinical studies are also required to determine how reactive aldehydes produced with the workplace environment, including hospitals, may potentially and more preferentially affect those with an ALDH2*2 variant. New therapeutic strategies should also be encouraged to prevent, minimize, and treat health-related disorders arising as a result of reactive aldehyde exposure. Together, considering the genetics of reactive aldehyde metabolism with respect to environmental sources of aldehyde exposure can lead to developing a basis for a precision medicine platform in the field of environmental health sciences.

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