Food and Chemical Toxicology 129 (2019) 38–53

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Mechanisms behind the atherothrombotic effects of acrolein, a review

Mohammad Reza Zirak[a,b], Soghra Mehri[a,b], Asieh Karimani[b], Majid Zeinali[b,c], A. Wallace Hayes[d,e], Gholamreza Karimi[a,b,*]

[a] Pharmaceutical Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Social Security Organization (SSO), Mashhad, Islamic Republic of Iran
[d] Harvard University, Cambridge, MA, USA
[e] Michigan State University, East Lansing, MI, USA

ARTICLE INFO

Keywords:
Acrolein
Atherosclerosis
Thrombosis
Dyslipidemia
Oxidative stress
Inflammation

ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. The majority of cardiovascular complications are secondary to atherosclerosis. Extensive evidence has showed that environmental pollutants such as cigarette smoke and automobile exhaust increase the risk of developing atherosclerosis. Acrolein, a highly reactive unsaturated aldehyde, is found as a contaminant in air, food and water. Investigations during the last decades have shown that acrolein via various mechanisms such as oxidative stress, enhancement of inflammatory processes and the activation of matrix metalloproteases can initiate and accelerate atherosclerotic lesions formation. Furthermore, exposure to acrolein has been suggested to induce or exacerbate systemic dyslipidemia, an important risk factor for the development of atherosclerosis. Finally, there are reports which indicate acrolein can increase platelet activation and stimulation of the coagulation cascade which subsequently leads to thrombosis. Even a modest reduction of pollutants such as acrolein can have substantial effects on population health. Public health efforts to reduce acrolein exposures from known sources may lower the prevalence of vascular disease. This review focuses on the potential pathways and mechanisms behind the acrolein-induced atherothrombotic effects.

1. Introduction

Cardiovascular diseases (CVDs) include a wide spectrum of disorders that affect the heart and blood vessels. It is the number one cause of death worldwide, with 17.5 million related deaths annually (31% of global deaths) (Stefanadis et al., 2017). The important CVDs include myocardial infarction (MI), angina pectoris (AP), heart failure (HF), stroke and hypertension (Lloyd-Jones et al., 2010). Although hypertension, obesity and metabolic disorders like diabetes and dyslipidemia are larger risk factors for CVDs, environmental factors such as air pollution and tobacco smoke impose additional synergistic or additive effects to these well-established risk factors (Bhatnagar, 2006; Jahani et al., 2018; Karbasforooshan and Karimi, 2017; Rempher, 2006).

Epidemiologic studies have reported that exposure to some chemicals and toxicants has been correlated with increasing the risk of CVDs (Brook et al., 2010; O'Toole et al., 2008). Air pollution is a complex mixture gases and particulates categorized according to median aerodynamic diameter of the different particulate matter (PM). Results of a large multicenter study in the US demonstrated that exposures to PM less than 2.5 μm ($PM_{2.5}$) was strongly associated with an increase in mortality risk (Zanobetti and Schwartz, 2009).

Likewise, tobacco smoke containing more than 7000 different chemicals, also contributes to cardiovascular injuries and death (Kelley et al., 2017; Rempher, 2006). Effort to identify the Hazard Index (HI) of mainstream smoke constituents showed that acrolein is a major cause of non-cancer untoward outcomes (88.5% of the overall theoretical HI) (Ezzati and Lopez, 2003; Haussmann, 2012). Similarly, the annual cardiovascular death rate due to smoking (1.69 million) is about equivalent to the smoking-related mortality due to lung cancer (0.97 million) and pulmonary diseases (0.85 million) combined (Haussmann, 2012).

Acrolein (2-propenal, CH2 = CHCHO) is a colorless, volatile liquid in pure form with an unpleasant odor [Fig. 1] (Arntz et al., 2000). Acrolein was first described in 1839 by Berzelius thorough degradation of glycerin (Stevens and Maier, 2008). It is found as a contaminant in food, air and water (Alwis et al., 2015). Generally, acrolein is formed from incomplete combustion of organic matters (like petrol, wood, plastic and tobacco) and in foods during high-temperature cooking

* Corresponding author. Pharmaceutical Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail address: KarimiG@mums.ac.ir (G. Karimi).

https://doi.org/10.1016/j.fct.2019.04.034
Received 8 December 2018; Received in revised form 18 March 2019; Accepted 18 April 2019
Available online 19 April 2019
0278-6915/

Abbreviations

3-HPMA	3-hydroxypropylmercapturic acid
ACS	Acute coronary syndromes
ADI	Acceptable Daily Intake
AP	Angina pectoris
APC	Activated protein C
Apo-B	Apolipoprotein-B
Apo-E	Apolipoprotein E
ASK-1	Apoptosis signal regulating kinase 1
ATF-2	Activator transcription factor-2
CD36	Cluster of differentiation 36
CHD	Coronary heart disease
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
CSF	Colony-stimulating factor
CVDs	Cardiovascular diseases
ECD	Endothelial cell dysfunction
EPA	Environmental Protection Agency
EPCs	Endothelial progenitor cells
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSH	Glutathione
HDL	High-density lipoprotein
HF	Heart failure
HI	Hazard Index
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HUVECs	Human umbilical vein endothelial cells
IDL	Intermediate-density lipoproteins
IKK	IκB kinase
IL-1β	Interleukin 1 beta
IL-8	Interleukin-8
I-κB	Inhibitor of kappa B
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDLr	Low density lipoprotein receptor
LOX-1	Lectin-like oxidized LDL receptor-1
MAP3K	Mitogen-activated protein kinase kinase kinase
MAPK	mitogen-activated protein kinase
MCP-1	Monocyte chemotactic protein-1
M-CSF	Macrophage colony-stimulating factor
MI	Myocardial infarction
MMPs	Matrix metalloproteinases
MPO	Myeloperoxidase
NA	Data not Available
NF-κB	nuclear factor-κB
NO	nitric oxide
OPMA	S-(3-oxopropyl)-N-acetylcysteine
Ox-LDL	Oxidized LDL
PEG2	Prostaglandin E2
PM	Particulate matter
PPARγ	Peroxisome proliferator activated receptor γ
P-SH	Protein sulfhydryl
RfC	reference concentration
ROS	Reactive oxygen species
SR-A1	Scavenger receptor class A type 1
TDI	Tolerable Daily Intake
TF	Tissue factor
TGF-β	Transforming growth factor beta
TIMP-3	Tissue inhibitor of metalloproteases-3
TNF-α	Tumor necrosis factor alpha
Trx	Thioredoxin
TrxR	Thioredoxin reductase
VSMCs	Vascular smooth muscle cells
XO	Xanthine oxidase

(Taghiabadi et al., 2012). Acrolein is produced endogenously from lipid peroxidation or polyamine metabolism; thereby being continuously generate in biological systems under oxidative stress (Lovell et al., 2000).

Acrolein, a ubiquitous environmental pollutant, may cause adverse effects in the central and peripheral nervous system (Butler et al., 2017; Valko et al., 2016), respiratory tract (Golden and Holm, 2017) and in various cardiovascular organs (Conklin, 2016; Conklin et al., 2017a). At the cellular level, acrolein causes toxic effects through enhancing of reactive oxygen species (ROS) (Uchida et al., 1998), DNA (Steiner et al., 2016; Tang et al., 2011) and protein adducts (Aldini et al., 2011), by induction of endoplasmic reticulum stress (ER) (Haberzettl et al., 2009) and immune dysfunction (Hristova et al., 2012) and by cell membrane damage and mitochondrial disruption (Sun et al., 2006).

Atherosclerosis is responsible for a large segment of CVD complications. Atherothrombosis is characterized by sudden atherosclerotic plaque or lesion disruption with superimposed thrombus formation. It may cause heart attack, peripheral artery disease and/or acute coronary syndromes (ACS) (Viles-Gonzalez et al., 2004).

DeJarnett et al. (2014) investigated the association between acrolein exposure and the risk of CVDs in humans. They found that the level of acrolein metabolite, 3-hydroxypropylmercapturic acid (3-HPMA) (Higashi et al., 2016) was correlated with increased risk of CVDs. In another study, it was reported that the plasma levels of protein-conjugated acrolein correlated with the development of carotid atherosclerosis (Yoshida et al., 2010). These findings supported by other evidences which show acrolein contributes in different steps of initiation and development of arthrosclerosis including damage to endothelial cells, modification of LDL, increase of inflammatory response and expression of scavenger receptors on the surface of macrophages which facilitates foam cell formation. More importantly, numerous studies have linked acrolein exposure to dyslipidemia, platelet activation and thrombosis; the well-known risk factors for cardiac and cerebral complications. In this review, we discussed the underlying mechanisms behind the atherosclerotic and thrombotic effects of acrolein.

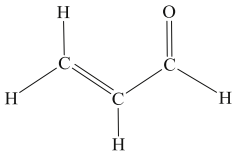

Fig. 1. Chemical structure of Acrolein.

2. Research methodology

Web of Sciences, PubMed, Scopus and Google Scholar databases comprising the date of publication from 1970 until November 2018 were searched. We extracted and reviewed the existing literature published by using the following keywords: “acrolein“, “2-propenal“, plus “atherosclerosis, “atherothrombotic“, “vascular“, “atherosclerotic”, “endothelial dysfunction“, “dyslipidemia”, “thrombosis”, and “inflammation”. Two hundred and twelve articles were found; the most relevant articles were selected for this review.

3. Acrolein sources and toxicokinetics

3.1. Acrolein sources of human exposure

The sources of acrolein that are most relevant to human exposure are dietary, endogenous and environmental sources (Fig. 2.). Briefly, incomplete combustion of organic substances, frying of foods in oils and endogenous lipid peroxidation are important sources of human exposure to acrolein. Food and environmental pollutants are the major sources of acrolein in human exposure and toxicity (Moghe et al., 2015). Endogenously, acrolein could be produced from metabolism of amino acids such as methionine and threonine (Fig. 3). Little is known about the amount of acrolein that produced within cells from these precursors.

A WHO working group established Tolerable Daily Intake (TDI) for acrolein is 7.5 μg/kg/day body weight (Abraham et al., 2011). The US EPA TDI is 0.5 μg/kg/day and the Acceptable Daily Intake (ADI) is 1.09 mg/day for oral exposure (EPA, 2004, 2018).

Acrolein is present in heated vegetable oils (Table 1). Depending on the type of oil, concentrations can range from 8.1 for coconut oil to 207.4 μg/kg for linseed oil after heating at 180 °C for 24 h (Ewert et al., 2011). If re-heated, these values can reach more than 10-fold higher (Yasuhara and Shibamoto, 1991). Overall, exposure to unsaturated aldehyde like acrolein through dietary consumption has been estimated to be nearly 5 mg/kg/day (Moghe et al., 2015; Wang et al., 2008). Acrolein exposure assessment was performed according to daily HPMA excretion (200–1000 μg/24 h) in urine of non-smokers (or former smokers on abstinence). Based on assumption that about 20% of acrolein intake excreted as 3-HPMA, in analogy to data obtained in rats, an estimate of acrolein exposure arrived at 300–1400 μg/d or 5–24 μg/kg body weight/day (Guth et al., 2013). If it was accepted that all foods have the highest reported level of acrolein, an exposure of around 1 mg/person/day (17 μg/kg b. w./day) may be estimated (Guth et al., 2013).

The U.S. Environmental Protection Agency (EPA) has reported that the main source of acrolein exposure of the general population is the atmosphere, which contains 8.2–24.6 μg/m^3 (DeWoskin et al., 2003). Combustion of vehicle fuels is a major source of anthropogenic atmospheric acrolein (Blair, 2016). The current best-established reference concentration (RfC) for acrolein is 0.02 μg/m^3 based on respiratory system impairment (Woodruff et al., 2007).

Cigarette smoke is another important source of acrolein exposure. Carmella and his colleagues (2007) reported that 3-HPMA, the main metabolite of acrolein, is significantly higher in smokers versus non-smokers.

Carbohydrates, triglycerides and glycerin were identified as the major precursors of acrolein in cigarettes (Figs. 4 and 5) (Piadé et al., 2013). Glycerin is added to cigarette tobacco to improve some characteristics such as moisture holding and as a surface active agent for flavors (Carmines and Gaworski, 2005).

Carbohydrates have considerable influence on acrolein production in cigarettes. Adding 16% sucrose to cigarettes led to an increase of nearly a two-fold increase in the content of acrolein (Stevens and Maier, 2008). Triglycerides are an indirect precursor of acrolein. Triglycerides hydrolysis produces glycerol; subsequently, glycerol can be converted to acrolein (Stevens and Maier, 2008).

Although electronic cigarette (e-cigarette) has developed to help smokers switch to less harmful forms of nicotine intake, research showed e-cigarette vapors may have considerable amount of toxic compounds (Farsalinos and Gillman, 2017). Some flavoring compounds like triacetin have been proposed working as precursors which increase the production of acrolein in e-cigarette (Vreeke et al., 2018). Propylene glycol and glycerol are the main sources that oxidized to toxic carbonyls compounds including formaldehyde, acetaldehyde and acrolein (Farsalinos and Gillman, 2017). Several factors such as voltage, temperature, ingredients of e-liquid and type of atomizer can affect the level of acrolein in e-cigarette. For example, voltage change from 3.3 to 4.8 V resulted an increased emission of acrolein up to 10-fold (Sleiman et al., 2016). Ogunwale et al. also reported that e voltage change from 11.7 to 16.6 V resulted an elevated emission up to 13-fold (Ogunwale et al., 2017). It was shown that overheating the e-cigarette liquid in way that produce “dry puff” could considerably enhance the aldehyde generation (Farsalinos et al., 2015a). Various studies indicated that the amount of acrolein which emitted with first generation of e-cigarette devices is more than next generations like 4th, probably because of controlling temperature in 4th generation and prevention of dry puff (Clapp and Jaspers, 2017; Flora et al., 2017). There are some studies which reported complex interaction among these factors. Study of Farsalinosa et al. demonstrated that with flavored liquids, increase of e-cigarette power will enhance acrolein emission while with liquids,

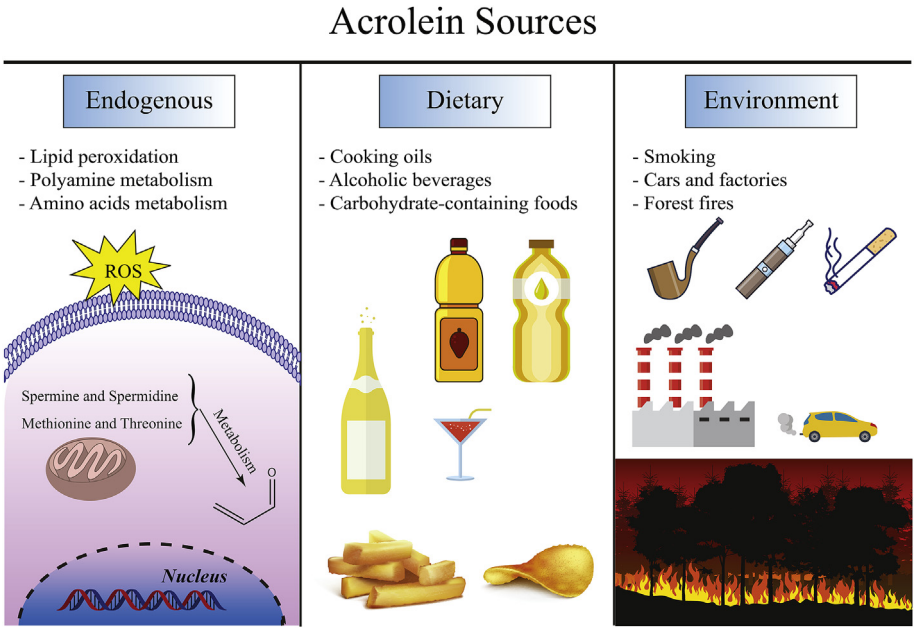

Fig. 2. Major sources of acrolein.

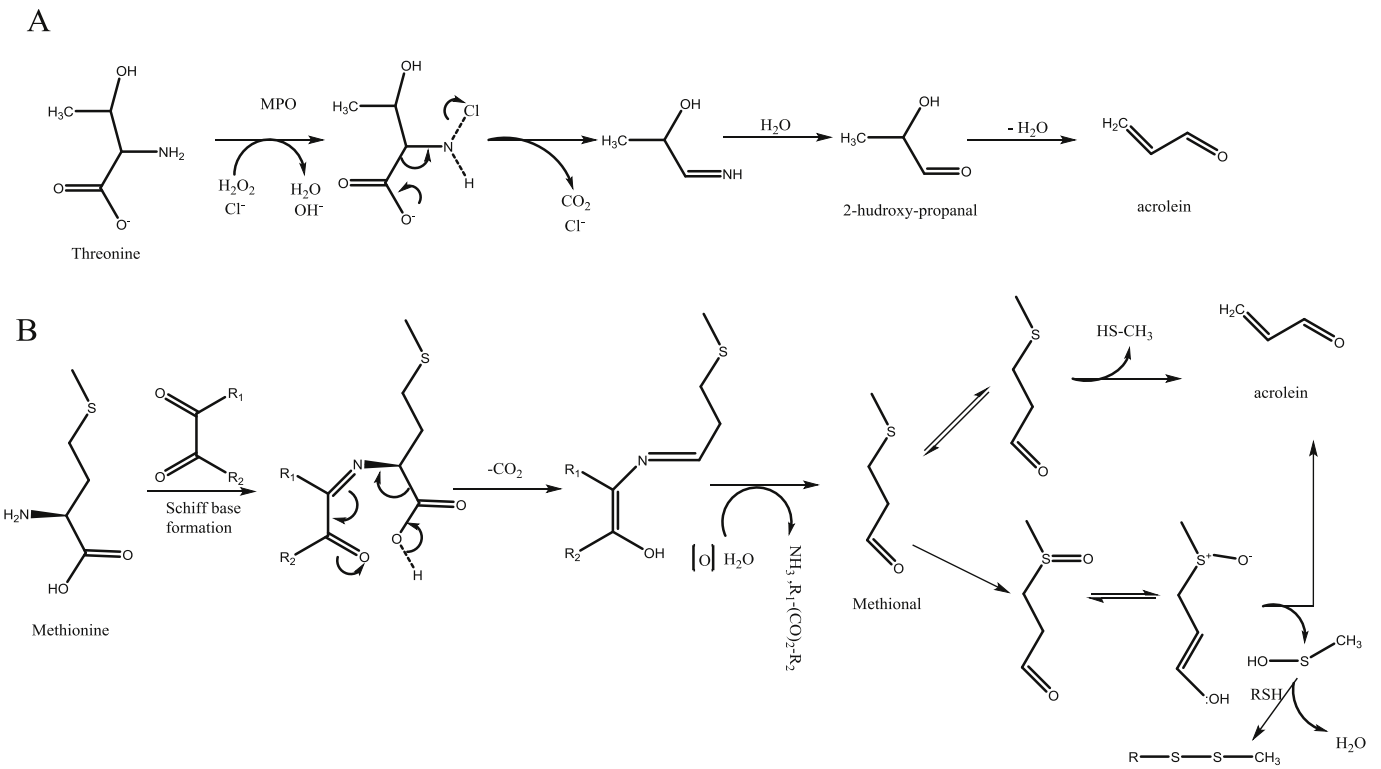

Fig. 3. Formation of acrolein from threonine (A) and methionine (B). Reproduced from (Stevens and Maier, 2008) with permission.

increase of e-cigarette power will decrease acrolein emission (Farsalinos et al., 2018a).

Some studies reported that in comparison with conventional cigarette, e-ciarette generally showed lower level of acrolein emission. Study of Goniewicz et al. indicated that switching from tobacco to e-cigarettes, substantially reduced exposure to toxicant like acrolein (Goniewicz et al., 2017). The similar results also were reported by other researchers (Farsalinos et al., 2018b; McRobbie et al., 2015; Ogunwale et al., 2017; Tayyarah and Long, 2014). In another study, Chen and his colleagues measured the health risk of e-cigarette versus conventional cigarette. They also reported exposure to various hazards including acrolein in conventional cigarette is higher than e-cigarette (Chen et al., 2017a).

The most common sources of human exposure to acrolein and the intake per day are summarized in Table 1 (Abraham et al., 2011; Guenther et al., 2013; Henning et al., 2017).

3.2. Toxicokinetics of acrolein

3.2.1. Absorption

Acrolein is well absorbed by inhalation exposure. Morris investigated the rate of absorption in exposed mice to 1.1 ppm and in rats to 0.9–9.1 ppm acrolein. Mice and rats absorbed 92% and 70–90% of inhaled acrolein via the upper respiratory tract (Morris, 1996; Morris et al., 2003). Similarly, acrolein seems to be well absorbed following dietary exposure. In a study conducted by Parent et al. (1996), 12–15% of a dose of 2.5 mg/kg and 28–31% of the initial dose of 15 mg/kg orally administered acrolein was found in the feces. In the other hand, approximately 70–88% of orally administered acrolein is absorbed with 12–31% of the orally administered dose being found in the feces (Parent et al., 1996). No study has measured the rate and extent of acrolein absorption after oral or inhalation exposure in humans (Registry, 2007).

3.2.2. Distribution

The disposition of [2,3–^{14}C] acrolein in rats after oral or intravenous administration was studied by Parent et al. Analysis of total radioactivity showed that acrolein was distributed in various organs including kidney, spleen, lungs, blood, liver, fat, adrenals, and ovaries 7 days after initial administration (Parent et al., 1996). The long time existence of acrolein in organs might be explained by this fact that acrolein binding to plasma proteins and hemoglobin is reversible, so acrolein could release from protein adducts and distributes to tissues (Kautiainen et al., 1989; Li et al., 2004).

3.2.3. Metabolism

Acrolein is highly soluble in water, alcohol and diethyl ether, so it can pass easily across the cell membrane by passive diffusion (Stevens and Maier, 2008). Acrolein is eliminated mostly via conjugation with glutathione (GSH) in the liver. After that, it undergoes enzymatic cleavage and N-acetylation to form S-(3-oxopropyl)-N-acetylcysteine (OPMA) in the kidney (Carmella et al., 2007).

Reduction of OPMA produces the main metabolite of acrolein, HPMA, which can be detected in urine. Moreover, oxidation of the aldehyde group yields *S*-carboxyethyl-*N*-acetylcysteine (carboxyethyl mercapturic acid) (Stevens and Maier, 2008). The major pathway for acrolein metabolism is illustrated in Fig. 6.

In addition, there is a minor metabolism pathway for acrolein. In this pathway, acrolein is converted by aldehyde dehydrogenases to acrylic acid (Kaye, 1973). Acrolein can also undergo enzyme-mediated epoxidation to yield glyceraldehyde (Patel et al., 1980).

Several studies have reported the half-life of acrolein in various matrixes. The half-life of acrolein has been reported in air (20 h–28 days), pond or river water (29 h) and portable or drinking water (11 days). (DeWoskin et al., 2003; EPA, 2003).

Although sensitive methods have been developed for measurement of acrolein in plasma and serum (Togashi et al., 2010, 2014), to best of our knowledge, the half-life of acrolein in plasma, has not been determined mainly due to binding to proteins.

3.2.4. Elimination and excretion

Results of a study by Parent et al. (1996) revealed that in rats fed

Table 1
The acrolein content of common sources that human may be exposed.

Source		Mean acrolein content	Daily intake		References
			Mixture (g or ml per day)	Acrolein (μg/day)	
Dietary	Vegetable oil (sunflower, soybeans and corn oil)	2.8–10.2 μg/L	50	0.14–0.51	(Osório and de Lourdes Cardeal, 2013a)
	Reheated corn oil	20.4 μg/L	NA	–	Yasuhara and Shibamoto (1991)
	Cocoa bean	0.25–0.45 μg/kg	NA	–	Żyżelewicz et al. (2017)
	Raw spirits	0.3–2.5 mg/dm3	NA	–	Curyło and Wardencki (2005)
	Wine	0.7–3.8 μg/L	43–400	Up to 1.5	Feron et al. (1991)
	Alcoholic beverages	247 μg/L	84–493	20.74–121.77	Kachele et al. (2014)
	Fruit spirits	591 μg/L	11–44	Up to 26	
	Grape narc	487 μg/L	NA	–	
	Whiskey	252 μg/L	Up to 180	Up to 45.36	
	Frying fats and oils	276 μg/L	50	13.8	
	Tequila	404 μg/L	NA	–	
	Fruits (apples, grapes, strawberries and blackberries)	10–50 μg/kg	337	3.37–16.85	Feron et al. (1991)
	Vegetables (cabbage, carrots, potatoes and tomatoes)	590 μg/kg	260–500	130–295	
	French-fried potatoes	3.25 μg/kg	NA	–	(Osório and de Lourdes Cardeal, 2011)
		14.8–19.9 μg/kg	NA	–	Ewert et al. (2014)
	Fried potato chips	16.3–23.3 μg/kg	NA	–	
	Fried donuts	14.1–16.9 μg/kg	NA	–	
Environmental	Electronic cigarette	1.22–16.21 μg/10 puffs	NA	–	Ogunwale et al. (2017)
		ND - 41.9 μg/150 puffs	NA	–	Lukasz et al. (2014)
		3.5 μg/puff	NA	–	Hutzler et al. (2014)
		0.19 μg/puff	NA	–	Tayyarah and Long (2014)
		0.5–13.5 ng/puff	NA	–	Geiss et al. (2015)
		ND - 2.5 ng/puff	NA	–	Geiss et al. (2016)
		0.13–3.7 μg/L	NA	–	Laugesen (2015)
		1μg/10 puffs	NA	–	Farsalinos et al. (2015b)
		ND - 1.97 μg/15 puffs	NA	–	Talih et al. (2016)
		Non-detected −1.34 μg/15 puffs	NA	–	Talih et al. (2017)
		ND - 24 μg/puff	NA	–	Uchiyama et al. (2016)
		1.31–3.44 μg/puff	NA	–	Khlystov and Samburova (2016)
		ND – 41.9 ng/puff	NA	–	Lee et al. (2018)
	Conventional cigarette	120.4 μg/10 puffs	NA	–	Farsalinos et al. (2015b)
		16.4 μg/puff	NA	–	Tayyarah and Long (2014)
		220–468 μg/cigarette	NA	–	Fujioka and Shibamoto (2006)
		10–20 μg/cigarette	NA	–	Pang and Lewis (2011)
		63 μg/cigarette	NA	–	Zhao et al. (2017)
		44–140 μg/cigarette	NA	–	Uchiyama et al. (2015)
		58–138 μg/cigarette	NA	–	Ding et al. (2016)
		47.1–50.3 μg/cigarette	NA	–	Dong and Moldoveanu (2004)
		54–155 μg/cigarette	NA	–	Roemer et al. (2004)
	Indoor air	< 0.5–29 μg/m3	NA	–	Faroon et al. (2008)
	Indoor air (restaurant kitchens and bakeries)	26.4–64.5 μg/m3	NA	–	Seaman et al. (2009)
	Outdoor air (United States)	0.0087–0.41 μg/m^3	NA	–	Woodruff et al. (2007)
	Outdoor air (Canada)	0.1–4.9 μg/m^3	NA	–	Gilbert et al. (2005)

NA, Data not Available, ND, Non-detected.

2.5 mg/kg [2,3–14C] acrolein, 27–31% of the initial dose was eliminated as CO_2 while 52–63% was excreted in the urine and 12–15% was excreted in the feces. Rats given 15 mg/kg [2,3–14C] acrolein showed a similar elimination pattern but with a lower % in the urine (37–41%) and a higher amount in the feces (28–31%).

4. Interaction of acrolein with macromolecules

Acrolein has strong electrophilic properties, so it can attack to various macromolecules such as DNA, lipids and proteins. As illustrated in Fig. 7, exocyclic amine of guanine residues serves as a strong Michael addition donor for the olefin double bond of acrolein (Tang et al., 2011). Tang et al. suggested that depends on environmental pH, γ-hydroxy-1, N2-propano-2′-deoxyguanosine (γ-OH-Acrolein-dG) adducts or α–OH-Acrolein-dG may be formed (Tang et al., 2011). Theses adducts interfere with DNA repair proteins and result in mutagenicity (Wang et al., 2012). In addition, acrolein could react with cysteine and lysine residues via two basic reactions: Michael addition and Schiff-base formation (Cai et al., 2009). Peptides with a free sulfhydryl group are highly susceptible to form a relatively stable adducts with acrolein (Cai et al., 2009). It should be noted the Michael addition reaction is reversible.

5. A brief summary of atherosclerosis pathophysiology

Atherosclerosis is a chronic inflammatory disease characterized by plaques built up inside arterial walls (de Winther et al., 2005). A plaque is typically composed of cholesterol, fat, calcium and other substances found in the circulating blood. Injury to the endothelial cells and endothelial dysfunction seems to be the first step in the development of atheromatous plaques formation (Boyle et al., 1997). This injury leads to change in endothelial permeability and infiltration and retention of

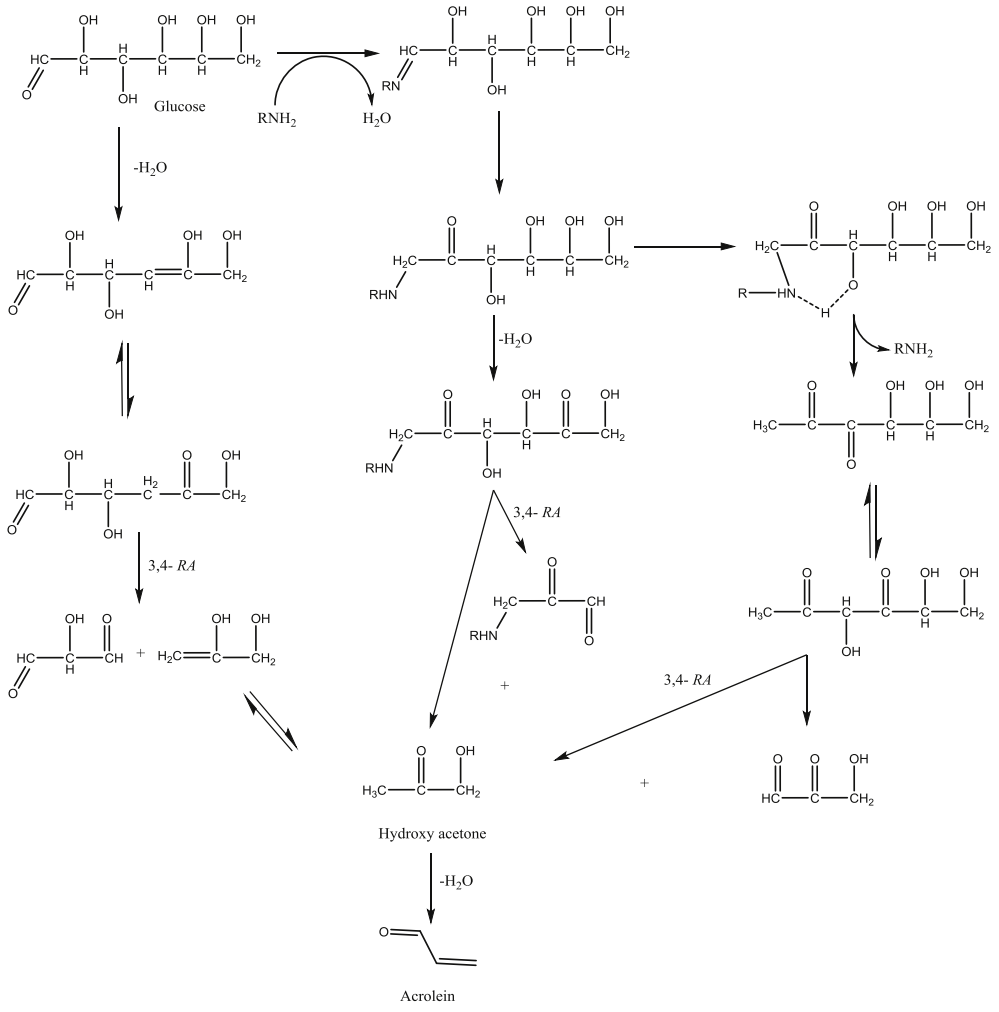

Fig. 4. Proposed pathways for acrolein formation from glucose. Reproduced from (Stevens and Maier, 2008) with permission. 3,4-RA; 3,4- retro aldol-cleavage.

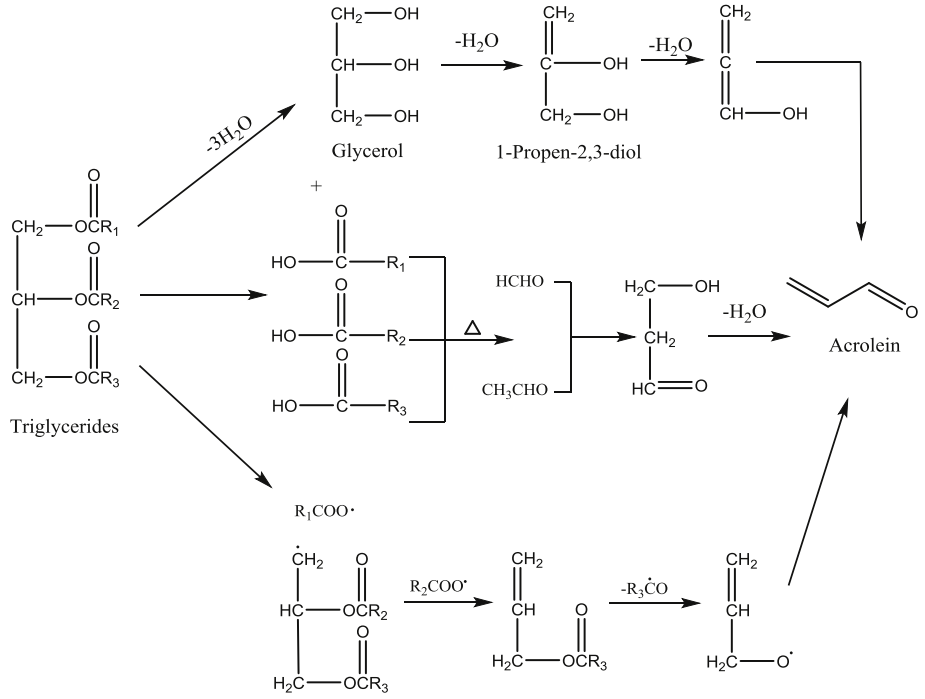

Fig. 5. Suggested pathways for acrolein formation from triglycerides. Reproduced from (Osório and de Lourdes Cardeal, 2013b) with permission.

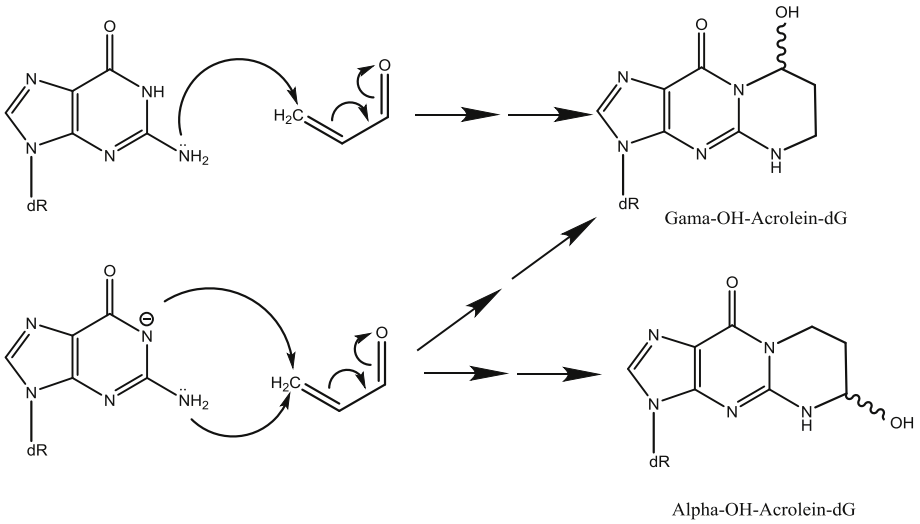

Fig. 6. Proposed mechanism for acrolein-DNA adduct formation. Reproduced from (Tang et al., 2011) with permission.

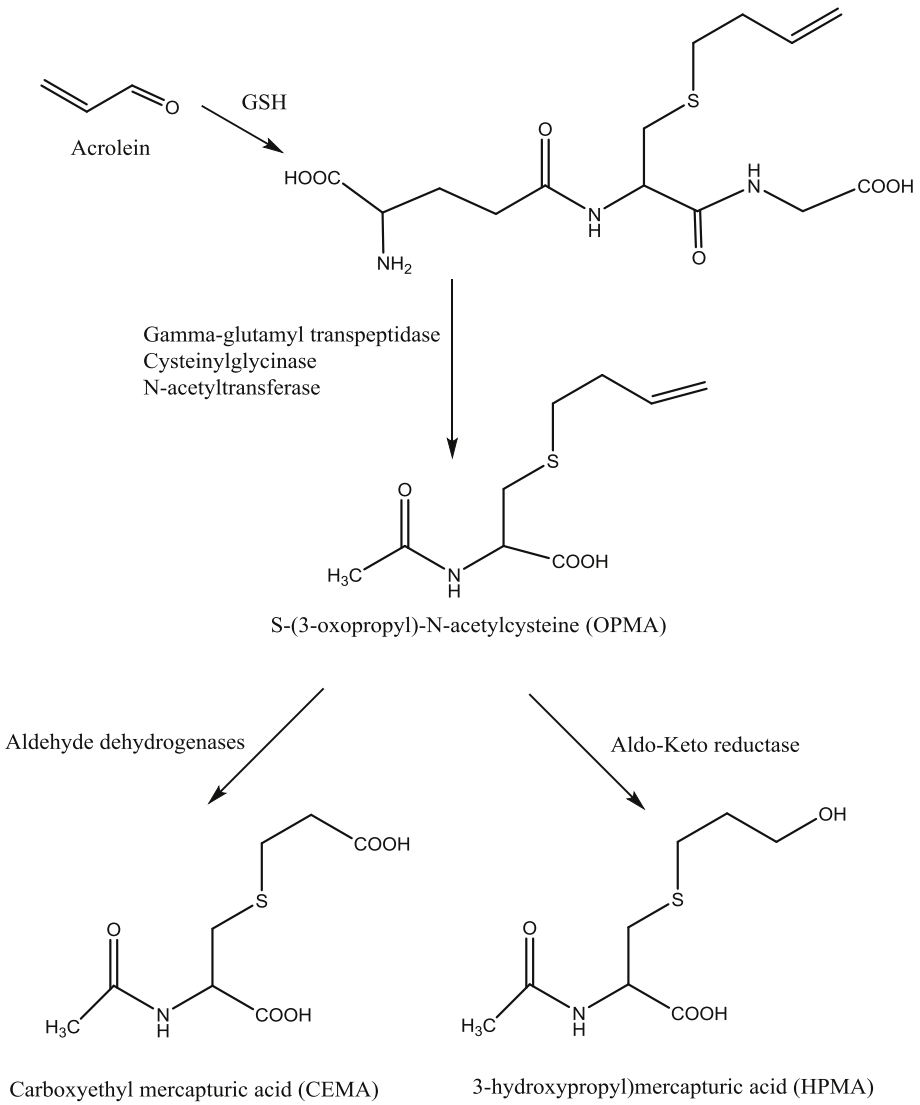

Fig. 7. Major pathway of acrolein metabolism. Reproduced from (Stevens and Maier, 2008) with permission.

lipoprotein particles, especially cholesterol-containing low-density lipoprotein (LDL) in the intima space (Plutzky, 2003). Trapped LDL in the intima leads to activation and release of several chemokines such as monocyte chemotactic protein-1 (MCP-1), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α) and IL-1β by endothelial cells which subsequently causes recruitment of monocyte and T cells from the blood to the sub-endothelial intima space (Aiello et al., 1999; Moore and Tabas, 2011).

LDL lipoproteins undergo oxidation by oxidizing enzyme including lipoxygenase and myeloperoxidase (MPO) that trigger its conversion into modified forms like oxidized LDL (ox-LDL) or acetylated LDL (McLaren et al., 2011; Yoshida and Kisugi, 2010). Monocytes are thought to differentiate into the various types of macrophages in the presence of some cytokines like macrophage colony-stimulating factor (M-CSF) and interleukins and LPS or in the presence of transforming growth factor beta (TGF-β) or glucocorticoid drugs (Ley et al., 2011).

Macrophages phagocytize ox-LDL or other modified lipoproteins to form foam cells. The foam cells are the hallmark of atherosclerotic lesions (Shao et al., 2016). Over time, with an increase in the number of foam cells, macrophage foam cells undergo apoptosis and form a necrotic core of atherosclerotic plaque (Moore and Tabas, 2011). These macrophages and endothelial cells release cytokines which cause more leucocytes entry into the intima from the systemic circulation. Consequently, vascular smooth muscle cells (VSMCs) proliferate and migrate into the intima, which finally constitutes “fatty streak”, the early visible lesions of atherosclerosis (Libby et al., 2002). After that, these fibrofatty materials and streaks combined to form an intermediate lesion of atherosclerosis, named fibrofatty streak. If the condition continues and risk factors exist, the lesion grows finally forming an atherosclerotic plaque. An atherosclerotic plaque has a fibrous cap covering a lipid-rich, necrotic core consisting of oxidized lipoproteins, cholesterol crystals, and cellular debris and different types of leucocytes. The culminating point of this slowly developing phenomenon often is plaque rupture or erosion, resulting in thrombosis and arterial occlusion.

Evidence accumulated in the last decade suggests that acrolein could affect almost all the steps of atherosclerotic lesion formation (Fig. 8).

6. Acrolein and atherosclerosis

6.1. Endothelial cell dysfunction

Endothelial cell dysfunction (ECD) is considered by many to be the critical step for the development of atherosclerosis (Dimmeler et al., 1998; Kockx and Herman, 2000; Yousefian et al., 2018).

Acrolein via several mechanisms can induce endothelial cell injury and death. A study by Chen et al. showed that acrolein exposure (5 mg/kg, gavage) can disrupt tight junction proteins that critically regulate epithelial paracellular permeability and subsequently trigger inflammatory responses (Chen et al., 2017b). Exposure of pulmonary artery endothelial cells to acrolein (1.5–25 μM) resulted in cytotoxicity to these cells which was associated with loss of glutathione (GSH) and protein sulfhydryl (P-SH) as well as a reduction in plasma membrane-specific Na^+/K^+-ATPase activity with an increase of lactate dehydrogenase (LDH) activity (Patel and Block, 1993). Also, acrolein has an inhibitory action on the thioredoxin reductase (TrxR)/thioredoxin (Trx) system, which plays a prominent role in maintenance of cellular thiol redox balance (Myers et al., 2011), so it could result in thiol redox imbalance, disruption in normal cell function and finally cell death (Szadkowski and Myers, 2008). Acrolein at 25 μM inhibited 88% of TrxR activity in human umbilical vein endothelial cells (HUVECs) (Park et al., 2005). Endothelial cell-specific deletion of thioredoxin-2 (Trx-2) resulted in events associated with atherosclerosis like ECD, increased vascular stiffness and a prothrombotic, proinflammatory vascular phenotype (Kirsch et al., 2016).

Acrolein (2.5–12.5 μM) can directly react with Trx to form Trx-S-acrolein adducts and this adduct would inhibit Trx activity (Myers and Myers, 2009). Inhibition of the TrxR/Trx system has several downstream effects relating to interference with TrxR/Trx function. For example, Trx in a reduced form binds to apoptosis signal-regulating kinase 1 (ASK1), a mitogen-activated protein kinase (MAP3K), and keeps ASK1 inactive (Saitoh et al., 1998). Acrolein also can block the inhibitory action of Trx on ASK1, therefore activatingASK1 indirectly (Myers and Myers, 2009). Activated ASK1 could mediate activation of the p38 MAPK and the c-junN-terminal-activating kinase and eventually triggering apoptosis pathways (Song et al., 2013a).

The endothelium controls vascular homeostasis via release of NO, prostaglandins, hyperpolarizing factors, endothelin, and low levels of ROS (Bronas and Dengel, 2010; Deanfield et al., 2007). Acrolein can produce oxidative stress and act as a perpetrator of oxidative stress

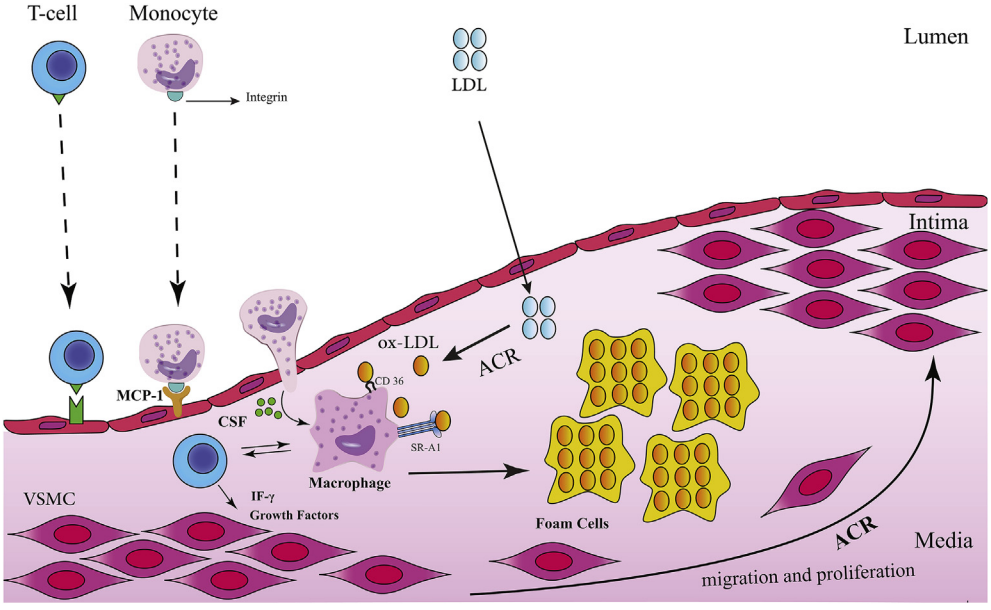

Fig. 8. Schematic representation of the arterial wall and sequence of development of atheroma plaque formation. Acrolein (ACR) participates in most steps of atherosclerosis include endothelial cell (EC) injury, expression of adhesion molecule like monocyte chemoattractant protein-1 (MCP-1) in ECs, diapedeses of monocytes and differentiation of them to macrophages, efflux of LDL or ox-LDL by macrophages to form foam cells and migration/proliferation of smooth muscle cell (SMC) to create a cap over foam cells.

which contributes to endothelial dysfunction (Uchida et al., 1998).

It has been shown that N-acetyl-L-cysteine or GSH administration fully restored cell growth when cell toxicity was induced by acrolein, so it seems oxidative stress and production of ROS is one of the major contributors for the cell toxicity of acrolein (Yoshida et al., 2009a).

Finally, *in vivo* evidence has shown that acrolein exposure decreased the number of circulating endothelial progenitor cells (EPCs) which are involved in vascular endothelial cell repair (Conklin et al., 2017b; Henning et al., 2017; Wheat et al., 2011).

6.2. Inflammation

Inflammation plays a central role in the pathogenesis of atherosclerosis and many clinical trials designed for treatment of atherosclerosis include inflammatory pathways as part of the protocol (Back and Hansson, 2015). However, controversy continues regarding the use of anti-inflammatory agents in the prevention and treatment of atherosclerosis (Libby et al., 2011). Damage to the endothelial cells by disturbing blood flow or from toxicant like acrolein are associated with changes in the morphology of endothelial cells which increase in turn the permeability to macromolecules such as LDL and other apolipoprotein-B (apo-B) containing lipoproteins (Bryan et al., 2014).

Acrolein can activate NF-κB, a major transcription factor which regulates inflammatory responses involved in atherosclerosis (de Winther et al., 2005; Sun et al., 2014; Yousefipour et al., 2017). Although, the inhibitory effect of acrolein on NF-κB has been reported previously (Aiello et al., 1999; Moon, 2011; Valacchi et al., 2004), it appears that the effect of acrolein on NF-κB depends on dose and duration of exposure and tissue type. In vessels, exposure to acrolein, leads to NF-κB activation (Haberzettl et al., 2009; Yousefipour and Newaz, 2011). NF-κB is a transcription factor that regulates a number of proteins linked to atherosclerosis including cytokines, chemokines, adhesion molecules and acute phase proteins. In addition, acrolein may play a role in important process like apoptosis and cell proliferation (de Winther et al., 2005). NF-κB exists in an inactive form in the cytoplasm and is associated with an inhibitory protein known as an inhibitor of kappa B (I-κB).

In the case of exposure of extracellular stimuli such as ROS, IL-s and certain foreign xenobiotics, IκB kinase (IKK) phosphorylates I-κB which may subsequently activate NF-κB. In such a way, NF-κB translocates to the nucleus, where it can activate transcription of a number of genes involved in atherosclerosis (de Winther et al., 2005).

Acrolein through several pathways may activate the NF-κB signaling cascades:

I) Acrolein conjugates to biomacromolecules and can produce excess amount of ROS which subsequently activates NF-κB (Agewall, 2006; Gloire et al., 2006; Yadav and Ramana, 2013). II) Acrolein increases the expression and production of inflammatory cytokine like TNF-α by affecting macrophages. This cytokine can activate NF-κB (Horton et al., 1999; Napetschnig and Wu, 2013; Song et al., 2013b). III) Acrolein can enhance total plasma cholesterol, an important factor that could activate NF-κB in the vessel wall (Conklin et al., 2011; Wilson et al., 2000). IV) Exposure to acrolein can induce ER stress and subsequently lead to NF-κB activation (Haberzettl et al., 2009).

V) Both clinical and experimental studies have shown that acrolein stimulates the synthesis of IL-6 and C-reactive protein (CRP) which contribute to activation of NF-κB (Abe et al., 2014; Liuzzo et al., 2007; Saiki et al., 2013; Yoshida et al., 2009b).

Extensive evidence revealed that ROS regulates the expression of genes involved in atherosclerosis by modulating various transcription factors, including the NF-κB and the peroxisome proliferator-activated receptor γ (PPARγ) (Napoli et al., 2001). NF-κB contributes to almost all steps of atherothrombotic lesion formation. NF-κB regulates several enzymes which cause modification of LDL to ox-LDL including 5-lipoxygenase (5-LPO), 12-LPO and cyclooxygenase-2 (COX-2) (de Winther et al., 2005). In a study by Kim et al., exposure to acrolein (1–10 μM) in murine macrophages led to increasing 5-LPO expression in a concentration-dependent manner through activation of the extracellular signal-regulated kinase (ERK) pathway (Kim et al., 2010). In another study, Park and colleagues showed that the treatment of HUVECs with 10 μmol/L acrolein increased the COX-2 expression and prostaglandin E2 (PGE2) production (Park et al., 2007). After that, to find out more about the exact mechanism, they treated HUVECs with inhibitors of ERK, JNK, and p38 MAPK. The levels of COX-2 mRNA were dramatically reduced by p38 MAPK inhibitor (SB203580) but not by ERK and JNK inhibitors (PD98059 and SP600125), respectively (Park et al., 2007). Furthermore, administration of acrolein to mice (4 mg/kg/i.p) resulted in induction of COX-2 in lung tissue (Park et al., 2007).

Taken together, it seems that acrolein contributes to LDL modification via NF-κB and ERK pathways. NF-κB could regulate chemokine expression such as MCP-1which is a chemokine for recruiting monocytes into the arterial sub endothelium (Harrington, 2000; Kim et al., 2006). MCP-1 deficient mice showed resistance against the development of atherosclerosis (Gu et al., 1998; Ohman et al., 2010). Interestingly, acrolein-modified proteins can augment the secretion of MCP-1 (Kirkham et al., 2003).

After infiltration of monocytes through the endothelial layer, they differentiated to macrophages under affecting colony-stimulating factors (CSF; M-CSF or CSF-1) (Hu et al., 2013). In this step, scavenger receptors like scavenger receptor class A type 1 (SR-A1), cluster of differentiation 36 (CD36) and lectin-like oxidized LDL receptor-1 (LOX-1) are highly expressed at the surface of macrophages. These receptors

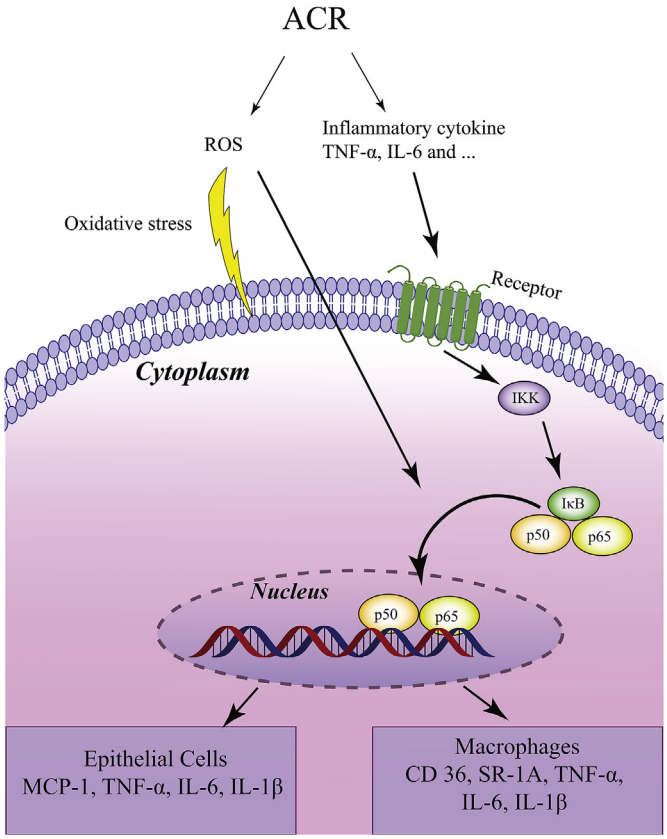

Fig. 9. The effect of acrolein (ACR) on epithelial cells and macrophages during atherosclerosis. On epithelial cells, acrolein can directly or via ROS cause damage to the endothelial cells. Acrolein also activates NF-κB leading to increase production of various pro-inflammatory cytokine and adhesion molecule like monocyte chemoattractant protein-1 (MCP-1) thereby recruiting monocytes to the site of the atheroma plaque. On the macrophages, acrolein increases expression of pro-inflammatory cytokine and scavenger receptor like CD36 and SR-A1 which are involved in LDL/ox-LDL phagocytosis by macrophages.

mediate ox-LDL phagocytosis by macrophages to form lipid-laden foam cells (Fig. 9) (Gistera and Hansson, 2017; Kunjathoor et al., 2002).

Acrolein exposure in a chamber (5 ppm, 6 h/day, for 3 days) in mice enhances the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) (Kasahara et al., 2008). Moreover, it has been reported that acrolein-conjugated LDL (Acro-LDL) not only upregulated the expression of SR-A1 on macrophages but also increased the accumulation of lipid droplets in macrophages, converting them into foam cells (Watanabe et al., 2013). It should be noted that acrolein-lysine adducts in LDL has been detected in atherosclerotic lesions in humans (Moghe et al., 2015). Although the experiments were not performed in atherosclerosis models, in other conditions, it was shown that acrolein exposure (0.5 μg/kg; 1 week) increased the expression of other scavenger receptors such as CD36 probably via the NF-κB pathway (Yousefipour et al., 2013).

In high-cholesterol diet-fed rabbits, Kanogawa's group showed that macrophages effectively phagocytes β-migrating very low-density lipoprotein conjugates with acrolein during atherosclerosis (Kanogawa et al., 2016).

Monocyte/macrophages and other leucocytes migrate into the intima, stimulating inflammatory cytokines and growth factors that lead to proliferation and migration of VSMCs from the media into the intima to form fibrous caps (Newby and Zaltsman, 1999).

VSMCs exist in diverse phenotype, ranging from contractile to synthetic (Rensen et al., 2007). The contractile phenotype present in normal blood cells has functions including regulation of blood vessel diameter (vasodilation and vasoconstriction) and blood flow (Louis and Zahradka, 2010). In response to injury and various stimuli like cytokines and growth factors, VSMCs undergo phenotypic switching and shift to a synthetic phenotype that proliferates to combat the negative situation (Doran et al., 2008).

MAPKs are another group of key regulatory proteins that control the VSMCs phenotype switch in responses to inflammation and stress signals (Zhang et al., 2017). Selective p38MAPK inhibitors, SB220025/SB203580, were shown to limit VSMCs proliferation (Jacob et al., 2005).

Studies indicated that cigarette smoke extract promotes vascular smooth muscle cell proliferation through ERK1/2- and NF-κB–dependent pathways (Chen et al., 2010; Starke et al., 2013; Xu et al., 2010; Yoshiyama et al., 2011). It has been reported that acrolein is one of the compound exist in high level in cigarette smoke extract (Lambert et al., 2005). Via similar mechanisms, the proliferation and migration of VSMCs is thought to be caused by acrolein (Cao et al., 2003; Ranganna et al., 2007; Yousefipour et al., 2005).

Ranganna et al. reported that exposure of VSMCs to anon-toxic dose of acrolein (2 μg/ml) resulted in activation of members of the MAPK family and protein tyrosine kinases including ERK1/2, p38MAPK SAPK/JNK and activator transcription factor-2 (ATF-2) (Ranganna et al., 2002). These researchers have shown acrolein-induced morphological changes in a concentration and time-dependent manner in their system. ROS has been identified as another factor that contributes to VSMCs proliferation via the p38 MAPK pathway (Su et al., 2001). Acrolein has also been shown to induce oxidative stress by depleting cellular glutathione and increasing ROS levels in VSMCs (Milton et al., 2015).

Inflammation is believed to play a key role in the progress of atherosclerotic plaque instability (Hansson et al., 2015). Analysis of autopsy and surgical specimens of human has revealed an increase in inflammatory activity including activated macrophages, mast cells and T cells as well as cytokine production in “vulnerable plaques” (Boyle, 1997; Maier et al., 2005; Moreno et al., 1994; van der Wal et al., 1994). Acrolein has been reported to increase inflammatory activity in atheroma plaques through activation of MAPK and NF-kB pathways (Borchers et al., 2009; Comer et al., 2014; Moretto et al., 2012; Park and Taniguchi, 2008). Overall, Moghe and colleagues suggested that dose and duration of acrolein exposure may have a significant effect on the outcome; exposure to acute high doses of acrolein likely suppresses innate and adaptive immune responses, facilitating develop of infection while chronic low-dose exposures may augment inflammatory responses leading to tissue injury (Moghe et al., 2015).

6.3. Extracellular matrix degradation

Matrix metalloproteinases (MMPs) are a group of proteinases that participate in the degradation of most extracellular matrix proteins (Brod et al., 2017). They can impact on the process of atherosclerotic lesion formation by facilitating various pathways such as collagenase activity or migration of VSMCs within a vessel, where they multiply and cause plaque formation (Agewall, 2006; Vacek et al., 2015).

The enhanced content and activity of MMP-1, -3, -8, -9, -12, and −13 have been observed in human atherosclerotic plaques (Gu et al., 2017). MMP-1 is a collagenase that expresses in atherosclerosis and aneurysms. Acrolein has been reported to induce MMP-1 in the aortic endothelium of rabbits by inhibiting the rapamycin pathway. Additionally, acrolein can down regulate the tissue inhibitor of metalloproteases-3 (TIMP-3), a major regulator of angiogenesis, in aortic endothelial cells. Acrolein might contribute to vascular diseases through enhanced MMP-1 and decreased TIMP-3 secretion in the endothelium, leading to impaired angiogenesis, matrix disruption, and vessel injury (Lemaître et al., 2011).

MMP-9 is another MMP that degrades extracellular matrixes such as elastin, proteoglycans, and collagen and facilitates migration of monocyte/macrophages into the intima (Yabluchanskiy et al., 2013).

Similarly, studies have indicated that acrolein exposure enhances MMP-9 activity in patients with primary Sjögren's syndrome or in MMP-9knockout mice (Deshmukh et al., 2008; Uemura et al., 2017). An increase in secretion of MMP-9 following acrolein exposure has been reported in lung epithelial cells (Dwivedi et al., 2018). Moreover, MMP-9 is critical for regulating the proliferation and migration of VSMCs into the intima (Mason et al., 1999). In a study by Cho and Reidy (2002), MMP-9 knockout mice showed a significant reduction in replication of VSMCs compared to wild-type. Several research teams have highlighted the fact that MMP-9 was also associated with coronary plaque instability (de Nooijer et al., 2006; Fan et al., 2014; Gough et al., 2006; Kobayashi et al., 2016). The increase of MMP-9 activity and/or expression might be another mechanism by which acrolein facilitates plaque rupturing (Noerager et al., 2015; Uemura et al., 2017; Zulueta et al., 2017). Study of O'Toole et al. revealed that acrolein exposure results in enhancement of MMP-9 secretion from macrophages via mechanisms including an increase in ROS generation, free intracellular calcium and xanthine oxidase (XO) activity (O'Toole et al., 2009).

7. Dyslipidemia

Acrolein can induce or exacerbate systemic dyslipidemia, an important risk factor for cardiovascular diseases (Plana et al., 2014). The effects of short-term oral exposure of acrolein on lipid profile and hepatic gene expression related to lipid metabolism and cytokines have been reported. Acrolein feeding (5 mg/kg) increased plasma cholesterol, triglycerides and VLDL with little change in LDL or HDL in mice. Shifts from small to large VLDL and from large to medium-small LDL with no change in the size of HDL particles also were observed by NMR analysis. Increased plasma VLDL levels led to a significant decrease in serum lipase activity and hepatic expression of hepatic lipase (Conklin et al., 2010). In another study, it was shown that oral acrolein exposureinduced3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase independent dyslipidemia apparently by changing the expression of the hepatic genes involved in lipid synthesis (Conklin et al., 2011).

Acrolein feeding not only increased the cholesterol level and the abundance of small and medium VLDL particles in the plasma, but also increased the atherosclerotic lesion formation in the aortic valve and in the aortic arch in mice (Srivastava et al., 2011).

Recently, Rom et al. reported that feeding Apolipoprotein E-deficient (apoE−/−) mice with acrolein resulted in a significant elevation in serum and aortic cholesterol, triglycerides and lipid peroxides (Rom et al., 2017).

Although oral exposure to acrolein induced dyslipidemia, inhalation exposure did not. Plasma levels of lipoproteins including cholesterol, HDL, LDL and triglycerides in both acute and sub-chronically acrolein-exposed mice were not statistically different from those exposed to filtered air (Sithu et al., 2010).

HDL can be chemically-modified by acrolein. The ability of HDL as a free cholesterol acceptor was significantly decreased in acrolein-modified HDL (acro-HDL) in contrast to native HDL. Indeed, acro-HDL promotes higher neutral lipid accumulation in murine macrophages. Acrolein modification of HDL produces a dysfunctional particle that may initiate atherogenesis by impairing functions that are crucial in the reverse cholesterol transport pathway (Chadwick et al., 2015). In another investigation, it was shown that acrolein could react with apoA-I, the major protein in HDL, thereby interfering with normal reverse cholesterol transport by HDL (Shao et al., 2005).

ApoE, as a part of intermediate-density lipoproteins (IDLs), mediates transport of cholesterol into brain and liver (Liu et al., 2013). Various studies have indicated apoE has a notable antiatherogenic function (Zhao et al., 2016). Two main mechanisms have been suggested for the antiatherogenic effects of apoE. First, it acts as a ligand for the low-density lipoprotein receptor (LDLr), which is involved in the transportation of VLDL and chylomicron remnants to the liver. Second, apoE reverses the process of cholesterol influx by macrophages to form foam cells (Hatters et al., 2006). Treatment of human or recombinant rat apoE with acrolein led to are duction in its ability to interact with lipid surfaces, cholesterol efflux, the LDLr- and heparin-binding capabilities and changing in the stability of the protein (Tamamizu-Kato et al., 2007; Tran et al., 2014). It seems that acrolein disrupts cholesterol homeostasis, leading to lipid dysregulation through these pathways. Interestingly, using immunoblot and immunohistochemical methods, acrolein–lysine adducts in plasma LDL and in the aorta were detected in cyclophosphamide-treated animals confirming the role of acrolein–lysine adducts in the development of atherosclerosis or atherogenesis (Arikketh et al., 2004).

8. Plaque rupturing and thrombosis

Plaque rupture and thrombosis formation on atherosclerotic lesions are associated with serious complications like coronary heart disease (CHD) or ischemic stroke (Bentzon et al., 2014; Chen et al., 2016; Naghavi et al., 2003).

Plaque composition and inflammation appear to be key factors that contribute to plaque instability and rupturing (Shah, 2007). In plaque rupture, loss of the fibrous cap results in exposure of the highly thrombogenic core to the circulating blood (Bentzon et al., 2014).

It has reported that mixtures containing acrolein like cigarette smoke increase the risk of acute rupture of a coronary atheromatous plaque (Barua and Ambrose, 2013; Gambardella et al., 2017). Acrolein via the same atherogenic mechanism may induce or exacerbate plaque destabilization and rupture.

Endothelial cells are the major barrier against thrombosis; therefore, their death may initiate the thrombosis process (Lafont, 2003). Xu et al. reported that an increase in endothelial apoptosis is correlated with the formation of thrombotic eroded plaques (Xu et al., 2009). Albrecht and colleagues (2017) have reported cytotoxicity and death of endothelial cells following acrolein exposure, even in low concentrations.

In addition, acrolein increases heart rate, blood pressure and vasospasm. Such mechanical stress has been postulated to induce rupture in vulnerable plaques (Garrett et al., 2008; Perez et al., 2013). These effects may be due to change of autonomic tone, specifically increased sympathetic input to the heart. It also has been suggested that the interaction among exposed atherosclerotic plaque component, platelet receptors and coagulation factors can lead to platelet activation, aggregation and the following formation of a thrombus (Badimon and Vilahur, 2014).

The pro-coagulant effects of acrolein and its suppressive effect on anticoagulant pathways in both cell-based and animal-based models were examined by measuring factors such as thrombin, activated protein C (APC) and tissue factor (TF). Exposure to acrolein increased thrombin generation in the plasma due to increasing TF activity in acrolein-treated cells (Swystun et al., 2011). Moreover, acrolein impacts the protein C anticoagulant pathway which could explain the increased risk of thrombosis observed in cancer patients receiving cyclophosphamide (Swystun et al., 2011). It should be noted that acrolein is a metabolite of cyclophosphamide that also can causes hemorrhagic cystitis and teratogenicity (Mirkes, 1985).

Although ROS was considered the major mechanism responsible for acrolein-induced cell damage, acrolein was shown to be more toxic than ROS (Igarashi et al., 2018). Cell damage caused by acrolein and ROS was compared during brain infarction, using a photochemically induced thrombosis mouse model (Saiki et al., 2009). By focusing on acrolein-conjugated albumin, it was shown that brain infarction correlates closely with acrolein because acrolein induces more severe cell damages compared with ROS (Saiki et al., 2011).

Some authors have proposed that acrolein could be used as a biomarker for early diagnosis of stroke (Igarashi and Kashiwagi, 2011; Tomitori et al., 2005; Yoshida et al., 2010), while the study of Nakamura et al. (2016) suggested that acrolein may take part in the development of stroke. Nakamura and his colleagues (2016) found that acrolein increased the size of brain infarction through augmentation of cytoplasmic Ca^{2+} in a mouse model of stroke.

Additionally, it has been reported that high acrolein concentration in serum adversely affects antithrombin activity. Antithrombin is one of the most important inhibitors of blood coagulation. Also, it has been reported that acrolein is three times more potent than homocysteine thiolactone, another potential marker of cardiovascular risk. These results could help explain the increased thrombogenicity in smokers and other conditions in which acrolein may be involved (Gugliucci, 2008).

9. Future perspectives

Acrolein, a ubiquitous environmental pollutant, classified by Environmental Protection Agency as a high-priority air/water toxicant (Aizenbud et al., 2016). Therefore, many efforts have done to delineate its precise mechanisms involved in the development of diseases such as spinal cord injury, diabetes mellitus, cardiovascular diseases, asthma, lung cancer and neurodegenerative diseases (Moghe et al., 2015).

It seems that oxidative stress and inflammatory signaling mediate the most adverse effect of acrolein in vascular system. Successful and effective methods have been introduced to remove or neutralize it from difference sources. Several studies show that compounds with antioxidant properties like α-tocopherol and polyphenolic compounds could decrease the level of acrolein formation (Ewert et al., 2014; Zamora et al., 2016; Zhu et al., 2009).

Hookah and cigarette smoke are another's important source of acrolein exposure (Cecil et al., 2017; Kassem et al., 2017). Morabito et al. developed a new charcoal loaded filters for cigarettes that reduced carbonyls in mainstream cigarette smoke (MSS) by nearly 99% (Morabito et al., 2017). Moreover, others filters including activated carbon (Polzin et al., 2008), ion-exchange resins with surface amine group (Branton et al., 2011) and synthetic polymer carbon (Nother et al., 2016) have been claimed to selectively filter harmful compounds from MSS. Kecili et al. described a simple and rapid approach for selective removal of acrolein from active pharmaceutical ingredients (APIs) by using PS-NH_2 and PS-trisamine (Kecili et al., 2012). The most effective scavenging activity was obtained with PS-NH2 which removed 97.8% of acrolein. Hydralazine, dimercaprol (BAL) and ascorbic acid

are other acrolein scavengers that have been demonstrated affordable efficacy (Tian and Shi, 2017; Zhu et al., 2011). Further research should focus on finding more effective methods for reducing human exposure to acrolein from known sources. For instance, better scavengers to remove acrolein in foods. The possible effects of acrolein on initiation of coagulation remain largely unexplored. The effects of acrolein on various factor involved in coagulation homeostasis including platelet adhesion and aggregation (Von Willebrand factor), antithrombotic (TF pathway inhibitor-1 [TFPI-1]) factors, as well as fibrinolytic (tissue-plasminogen activator [t-PA]) and antifibrinolytic factors (plasminogen activator inhibitor-1 [PAI-1]) have not been appropriately investigated. More research is needed to identify the exact effect of acrolein on plaque stability. Oxidative stress and ROS production, as well as inflammatory signaling, mediate most of the adverse effects of acrolein in vascular system. Therefore, using antioxidants might be a potential solution to counteract acrolein toxicity.

10. Conclusion

Acrolein is a ubiquitous environmental pollutant classified by EPA as a high-priority air/water toxicant. In the current review, we suggest how acrolein, a major toxic component of cigarette smoke and air pollution, may be involved in different steps of atherosclerosis initiation, progression and rupture often resulting in life threatening condition like stroke and myocardial infarction. Acrolein could interrupt endothelial cell permeability, initiate and exacerbate inflammation in the intima and degrade of the extracellular matrix by activation of MMPs to facilitate atheroma plaque formation. Moreover, we showed how acrolein may cause change in lipid profile which increases the risk of atherosclerosis. Finally, acrolein may contribute in the plaque instability and formation of thrombosis. Some studies reported effective scavenger of acrolein in some matrix like food but the efficacy of these scavengers in prevention of the harmful effect of acrolein remain to be explored.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

The authors are thankful to the Vice Chancellor of Research, Mashhad University of Medical Sciences for financial support.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.04.034.

References

Abe, A., Nishiyama, Y., Harada-Abe, M., Okubo, S., Ueda, M., Mishina, M., Katayama, Y., 2014. Relative risk values of age, acrolein, IL-6 and CRP as markers of periventricular hyperintensities: a cross-sectional study. BMJ Open 4, 1–6.

Abraham, K., Andres, S., Palavinskas, R., Berg, K., Appel, K.E., Lampen, A., 2011. Toxicology and risk assessment of acrolein in food. Mol. Nutr. Food Res. 55, 1277–1290.

Agewall, S., 2006. Matrix metalloproteinases and cardiovascular diseaseThe opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology. Eur. Heart J. 27, 121–122.

Aiello, R.J., Bourassa, P.-A.K., Lindsey, S., Weng, W., Natoli, E., Rollins, B.J., Milos, P.M., 1999. Monocyte chemoattractant protein-1 accelerates atherosclerosis in apolipoprotein E-deficient mice. Arterioscler. Thromb. Vasc. Biol. 19, 1518.

Aizenbud, D., Aizenbud, I., Reznick, A.Z., Avezov, K., 2016. Acrolein—an α,β-unsaturated aldehyde: a review of oral cavity exposure and oral pathology effects. Rambam Maimonides Med. J. 7, e0024.

Albrecht, T., Schilperoort, M., Zhang, S., Braun, J.D., Qiu, J., Rodriguez, A., Pastene, D.O., Kramer, B.K., Koppel, H., Baelde, H., de Heer, E., Anna Altomare, A., Regazzoni, L., Denisi, A., Aldini, G., van den Born, J., Yard, B.A., Hauske, S.J., 2017. Carnosine attenuates the development of both type 2 diabetes and diabetic nephropathy in BTBR ob/ob mice. Sci. Rep. 7, 44492.

Aldini, G., Orioli, M., Carini, M., 2011. Protein modification by acrolein: relevance to pathological conditions and inhibition by aldehyde sequestering agents. Mol. Nutr. Food Res. 55, 1301–1319.

Alwis, K.U., deCastro, B.R., Morrow, J.C., Blount, B.C., 2015 Dec. Acrolein exposure in U.S. Tobacco smokers and non-tobacco users: NHANES 2005-2006. Environ. Health Perspect. 123 (12), 1302–1308.

Arikketh, D., Niranjali, S., Devaraj, H., 2004. Detection of acrolein–lysine adducts in plasma low-density lipoprotein and in aorta of cyclophosphamide-administered rats. Arch. Toxicol. 78, 397–401.

Arntz, D., Fischer, A., Höpp, M., Jacobi, S., Sauer, J., Ohara, T., Sato, T., Shimizu, N., Schwind, H., 2000. Acrolein and Methacrolein, Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH Verlag GmbH & Co. KGaA.

Back, M., Hansson, G.K., 2015. Anti-inflammatory therapies for atherosclerosis. Nat. Rev. Cardiol. 12, 199–211.

Badimon, L., Vilahur, G., 2014. Thrombosis formation on atherosclerotic lesions and plaque rupture. J. Intern. Med. 276, 618–632.

Barua, R.S., Ambrose, J.A., 2013. Mechanisms of coronary thrombosis in cigarette smoke exposure. Arterioscler. Thromb. Vasc. Biol. 33, 1460–1467.

Bentzon, J.F., Otsuka, F., Virmani, R., Falk, E., 2014. Mechanisms of plaque formation and rupture. Circ. Res. 114, 1852–1866.

Bhatnagar, A., 2006. Environmental cardiology: studying mechanistic links between pollution and heart disease. Circ. Res. 99, 692–705.

Blair, L., 2016. Assessment Report on Acrolein for Developing Ambient Air Quality Objectives. Meridian Environmental Inc., Edmonton, Canada.

Borchers, M.T., Wesselkamper, S.C., Deshmukh, H., Beckman, E., Medvedovic, M., Sartor, M., Leikauf, G.D., 2009. The role of T cells in the regulation of acrolein-induced pulmonary inflammation and epithelial-cell pathology. Res. Rep. Health Eff. Inst. 146, 5–29.

Boyle, J.J., 1997. Association of coronary plaque rupture and atherosclerotic inflammation. J. Pathol. 181, 93–99.

Boyle Jr., M.D.E.M., Lille Md, S.T., Allaire Md, E., Clowes Md, A.W., Verrier Md, E.D., 1997. Endothelial cell injury in cardiovascular surgery: atherosclerosis 1. Ann. Thorac. Surg. 63, 885–894.

Branton, P.J., McAdam, K.G., Winter, D.B., Liu, C., Duke, M.G., Proctor, C.J., 2011. Reduction of aldehydes and hydrogen cyanide yields in mainstream cigarette smoke using an amine functionalised ion exchange resin. Chem. Cent. J. 5 15-15.

Brod, J.M., Demasi, A.P.D., Montalli, V.A., Teixeira, L.N., Furuse, C., Aguiar, M.C., Soares, A.B., Sperandio, M., Araujo, V.C., 2017. Nrf2-peroxiredoxin I axis in polymorphous adenocarcinoma is associated with low matrix metalloproteinase 2 level. Virchows Arch. 471, 793–798.

Bronas, U.G., Dengel, D.R., 2010. Influence of vascular oxidative stress and inflammation on the development and progression of atherosclerosis. Am. J. Lifestyle Med. 4, 521–534.

Brook, R.D., Rajagopalan, S., Pope, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., Holguin, F., Hong, Y., Luepker, R.V., Mittleman, M.A., Peters, A., Siscovick, D., Smith, S.C., Whitsel, L., Kaufman, J.D., Epidemiology, o.b.o.t.A.H.A.C.o., Prevention, C.o.t.K.i.C.D., Council on Nutrition, P.A., Metabolism, 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American heart association. Circulation 121, 2331–2378.

Bryan, M.T., Duckles, H., Feng, S., Hsiao, S.T., Kim, H.R., Serbanovic-Canic, J., Evans, P.C., 2014. Mechanoresponsive networks controlling vascular inflammation. Arterioscler. Thromb. Vasc. Biol. 34, 2199.

Butler, B., Acosta, G., Shi, R., 2017. Exogenous Acrolein intensifies sensory hypersensitivity after spinal cord injury in rat. J. Neurol. Sci. 379, 29–35.

Cai, J., Bhatnagar, A., Pierce Jr., W.M., 2009. Protein modification by acrolein: formation and stability of cysteine adducts. Chem. Res. Toxicol. 22, 708–716.

Cao, Z., Hardej, D., Trombetta, L.D., Trush, M.A., Li, Y., 2003. Induction of cellular glutathione and glutathione S-transferase by 3H-1,2-dithiole-3-thione in rat aortic smooth muscle A10 cells: protection against acrolein-induced toxicity. Atherosclerosis 166, 291–301.

Carmella, S.G., Chen, M., Zhang, Y., Zhang, S., Hatsukami, D.K., Hecht, S.S., 2007. Quantitation of acrolein-derived (3-hydroxypropyl)mercapturic acid in human urine by liquid Chromatography – Atmospheric pressure chemical ionization tandem mass Spectrometry: effects of cigarette smoking. Chem. Res. Toxicol. 20, 986–990.

Carmines, E.L., Gaworski, C.L., 2005. Toxicological evaluation of glycerin as a cigarette ingredient. Food Chem. Toxicol. 43, 1521–1539.

Cecil, T.L., Brewer, T.M., Young, M., Holman, M.R., 2017. Acrolein yields in mainstream smoke from commercial cigarette and little cigar tobacco products. Nicotine Tob. Res. 19, 865–870.

Chadwick, A.C., Holme, R.L., Chen, Y., Thomas, M.J., Sorci-Thomas, M.G., Silverstein, R.L., Pritchard Jr., K.A., Sahoo, D., 2015. Acrolein impairs the cholesterol transport functions of high density lipoproteins. PLoS One 10, e0123138.

Chen, J., Bullen, C., Dirks, K., 2017a. A comparative health risk assessment of electronic cigarettes and conventional cigarettes. Int. J. Environ. Res. Public Health 14.

Chen, Q.-w., Edvinsson, L., Xu, C.-B., 2010. Cigarette smoke extract promotes human vascular smooth muscle cell proliferation and survival through ERK1/2- and NF-κB–dependent pathways. Sci. World J. 10.

Chen, W.-Y., Wang, M., Zhang, J., Barve, S.S., McClain, C.J., Joshi-Barve, S., 2017b. Acrolein disrupts tight junction proteins and causes endoplasmic reticulum stress-mediated epithelial cell death leading to intestinal barrier dysfunction and permeability. Am. J. Pathol. 187, 2686–2697.

Chen, Y.C., Huang, A.L., Kyaw, T.S., Bobik, A., Peter, K., 2016. Atherosclerotic plaque rupture: identifying the straw that breaks the camel's back. Arterioscler. Thromb. Vasc. Biol. 36, e63–72.

Cho, A., Reidy, M.A., 2002. Matrix metalloproteinase-9 is necessary for the regulation of

smooth muscle cell replication and migration after arterial injury. Circ. Res. 91, 845–851.
Clapp, P.W., Jaspers, I., 2017. Electronic cigarettes: their constituents and potential links to asthma. Curr. Allergy Asthma Rep. 17, 79.
Comer, D.M., Elborn, J.S., Ennis, M., 2014. Inflammatory and cytotoxic effects of acrolein, nicotine, acetylaldehyde and cigarette smoke extract on human nasal epithelial cells. BMC Pulm. Med. 14, 32.
Conklin, D.J., 2016. Acute cardiopulmonary toxicity of inhaled aldehydes: role of TRPA1. Ann. N. Y. Acad. Sci. 1374, 59–67.
Conklin, D.J., Barski, O.A., Lesgards, J.-F., Juvan, P., Rezen, T., Rozman, D., Prough, R.A., Vladykovskaya, E., Liu, S., Srivastava, S., 2010. Acrolein consumption induces systemic dyslipidemia and lipoprotein modification. Toxicol. Appl. Pharmacol. 243, 1–12.
Conklin, D.J., Haberzettl, P., Jagatheesan, G., Kong, M., Hoyle, G.W., 2017a. Role of TRPA1 in acute cardiopulmonary toxicity of inhaled acrolein. Toxicol. Appl. Pharmacol. 324, 61–72.
Conklin, D.J., Malovichko, M.V., Zeller, I., Das, T.P., Krivokhizhina, T.V., Lynch, B.H., Lorkiewicz, P., Agarwal, A., Wickramasinghe, N., Haberzettl, P., Sithu, S.D., Shah, J., O'Toole, T.E., Rai, S.N., Bhatnagar, A., Srivastava, S., 2017b. Biomarkers of chronic acrolein inhalation exposure in mice: implications for tobacco product-induced toxicity. Toxicol. Sci. 158, 263–274.
Conklin, D.J., Prough, R.A., Juvan, P., Rezen, T., Rozman, D., Haberzettl, P., Srivastava, S., Bhatnagar, A., 2011. Acrolein-induced dyslipidemia and acute-phase response are independent of HMG-CoA reductase. Mol. Nutr. Food Res. 55, 1411–1422.
Curyło, J., Wardencki, W., 2005. Determination of acetaldehyde and acrolein in raw spirits by capillary isotachophoresis after derivatization. Anal. Lett. 38, 1659–1669.
de Nooijer, R., Verkleij, C.J., von der Thusen, J.H., Jukema, J.W., van der Wall, E.E., van Berkel, T.J., Baker, A.H., Biessen, E.A., 2006. Lesional overexpression of matrix metalloproteinase-9 promotes intraplaque hemorrhage in advanced lesions but not at earlier stages of atherogenesis. Arterioscler. Thromb. Vasc. Biol. 26, 340–346.
de Winther, M.P.J., Kanters, E., Kraal, G., Hofker, M.H., 2005. Nuclear Factor κB signaling in atherogenesis. Arterioscler. Thromb. Vasc. Biol. 25, 904–914.
Deanfield, J.E., Halcox, J.P., Rabelink, T.J., 2007. Endothelial function and dysfunction: testing and clinical relevance. Circulation 115, 1285–1295.
DeJarnett, N., Conklin, D.J., Riggs, D.W., Myers, J.A., O'Toole, T.E., Hamzeh, I., Wagner, S., Chugh, A., Ramos, K.S., Srivastava, S., Higdon, D., Tollerud, D.J., DeFilippis, A., Becher, C., Wyatt, B., McCracken, J., Abplanalp, W., Rai, S.N., Ciszewski, T., Xie, Z., Yeager, R., Prabhu, S.D., Bhatnagar, A., 2014. Acrolein exposure is associated with increased cardiovascular disease risk. J. Am. Heart Assoc. 3, e000934.
Deshmukh, H.S., Shaver, C., Case, L.M., Dietsch, M., Wesselkamper, S.C., Hardie, W.D., Korfhagen, T.R., Corradi, M., Nadel, J.A., Borchers, M.T., Leikauf, G.D., 2008. Acrolein-activated matrix metalloproteinase 9 contributes to persistent mucin production. Am. J. Respir. Cell Mol. Biol. 38, 446–454.
DeWoskin, R., Greenberg, M., Pepelko, W., Strickland, J., 2003. Toxicological Review of Acrolein. US Environmental Protection Agency, Washington, DC, pp. 1–99.
Dimmeler, S., Hermann, C., Zeiher, A.M., 1998. Apoptosis of endothelial cells. Contribution to the pathophysiology of atherosclerosis? Eur. Cytokine Netw. 9, 697–698.
Ding, Y.S., Yan, X., Wong, J., Chan, M., Watson, C.H., 2016. In situ derivatization and quantification of seven carbonyls in cigarette mainstream smoke. Chem. Res. Toxicol. 29, 125–131.
Dong, J.Z., Moldoveanu, S.C., 2004. Gas chromatography-mass spectrometry of carbonyl compounds in cigarette mainstream smoke after derivatization with 2,4-dinitrophenylhydrazine. J. Chromatogr. A 1027, 25–35.
Doran, A.C., Meller, N., McNamara, C.A., 2008. The role of smooth muscle cells in the initiation and early progression of atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 28, 812–819.
Dwivedi, A.M., Upadhyay, S., Johanson, G., Ernstgård, L., Palmberg, L., 2018. Inflammatory effects of acrolein, crotonaldehyde and hexanal vapors on human primary bronchial epithelial cells cultured at air-liquid interface. Toxicol. Vitro 46, 219–228.
EPA, U.S., 2003. Toxicological Review of Acrolein. US EPA, pp. 5–7.
EPA, U.S., 2004. Health and Environmental Effects Profile for Acrolein. U.S. Environmental Protection Agency, Washington, D.C.
EPA, U.S., 2018. Non-Carcinogen Tolerable Daily Intake (TDI) Values from. US EPA.
Ewert, A., Granvogl, M., Schieberle, P., 2011. Development of two stable isotope dilution assays for the quantitation of acrolein in heat-processed fats. J. Agric. Food Chem. 59, 3582–3589.
Ewert, A., Granvogl, M., Schieberle, P., 2014. Isotope-labeling studies on the formation pathway of acrolein during heat processing of oils. J. Agric. Food Chem. 62, 8524–8529.
Ezzati, M., Lopez, A.D., 2003. Estimates of global mortality attributable to smoking in 2000. Lancet 362, 847–852.
Fan, X., Wang, E., Wang, X., Cong, X., Chen, X., 2014. MicroRNA-21 is a unique signature associated with coronary plaque instability in humans by regulating matrix metalloproteinase-9 via reversion-inducing cysteine-rich protein with Kazal motifs. Exp. Mol. Pathol. 96, 242–249.
Faroon, O., Roney, N., Taylor, J., Ashizawa, A., Lumpkin, M.H., Plewak, D.J., 2008. Acrolein environmental levels and potential for human exposure. Toxicol. Ind. Health 24, 543–564.
Farsalinos, K.E., Gillman, G., 2017. Carbonyl emissions in E-cigarette aerosol: a systematic review and methodological considerations. Front. Physiol. 8, 1119.
Farsalinos, K.E., Kistler, K.A., Pennington, A., Spyrou, A., Kouretas, D., Gillman, G., 2018a. Aldehyde levels in e-cigarette aerosol: findings from a replication study and from use of a new-generation device. Food Chem. Toxicol. 111, 64–70.
Farsalinos, K.E., Voudris, V., Poulas, K., 2015a. E-cigarettes generate high levels of aldehydes only in 'dry puff' conditions. Addiction 110, 1352–1356.
Farsalinos, K.E., Voudris, V., Poulas, K., 2015b. E-cigarettes generate high levels of aldehydes only in 'dry puff' conditions. Addiction 110, 1352–1356.
Farsalinos, K.E., Yannovits, N., Sarri, T., Voudris, V., Poulas, K., Leischow, S.J., 2018b. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction 113, 2099–2106.
Feron, V.J., Til, H.P., de Vrijer, F., Woutersen, R.A., Cassee, F.R., van Bladeren, P.J., 1991. Aldehydes: occurrence, carcinogenic potential, mechanism of action and risk assessment. Mutat. Res. Genet. Toxicol. 259, 363–385.
Flora, J.W., Wilkinson, C.T., Wilkinson, J.W., Lipowicz, P.J., Skapars, J.A., Anderson, A., Miller, J.H., 2017. Method for the determination of carbonyl compounds in e-cigarette aerosols. J. Chromatogr. Sci. 55, 142–148.
Fujioka, K., Shibamoto, T., 2006. Determination of toxic carbonyl compounds in cigarette smoke. Environ. Toxicol. 21, 47–54.
Gambardella, J., Sardu, C., Sacra, C., Del Giudice, C., Santulli, G., 2017. Quit smoking to outsmart atherogenesis: molecular mechanisms underlying clinical evidence. Atherosclerosis 257, 242–245.
Garrett, M.C., McCullough-Hicks, M.E., Kim, G.H., Komotar, R.J., Kellner, C.P., Hahn, D.K., Otten, M.L., Rynkowski, M.A., Merkow, M.B., Starke, R.M., Connolly, E.S., 2008. Plasma acrolein levels and their association with delayed ischemic neurological deficits following aneurysmal subarachnoid haemorrhage: a pilot study. Br. J. Neurosurg. 22, 546–549.
Geiss, O., Bianchi, I., Barahona, F., Barrero-Moreno, J., 2015. Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes. Int. J. Hyg Environ. Health 218, 169–180.
Geiss, O., Bianchi, I., Barrero-Moreno, J., 2016. Correlation of volatile carbonyl yields emitted by e-cigarettes with the temperature of the heating coil and the perceived sensorial quality of the generated vapours. Int. J. Hyg Environ. Health 219, 268–277.
Gilbert, N.L., Guay, M., David Miller, J., Judek, S., Chan, C.C., Dales, R.E., 2005. Levels and determinants of formaldehyde, acetaldehyde, and acrolein in residential indoor air in Prince Edward Island, Canada. Environ. Res. 99, 11–17.
Gistera, A., Hansson, G.K., 2017. The immunology of atherosclerosis. Nat. Rev. Nephrol. 13, 368–380.
Gloire, G., Legrand-Poels, S., Piette, J., 2006. NF-κB activation by reactive oxygen species: fifteen years later. Biochem. Pharmacol. 72, 1493–1505.
Golden, R., Holm, S., 2017. Indoor air quality and asthma: has unrecognized exposure to acrolein confounded results of previous studies? Dose-Response 15, 1–9.
Goniewicz, M.L., Gawron, M., Smith, D.M., Peng, M., Jacob 3rd, P., Benowitz, N.L., 2017. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: a longitudinal within-subjects observational study. Nicotine Tob. Res. : Off. J. Soc. Res. Nicotine Tob. 19, 160–167.
Gough, P.J., Gomez, I.G., Wille, P.T., Raines, E.W., 2006. Macrophage expression of active MMP-9 induces acute plaque disruption in apoE-deficient mice. J. Clin. Investig. 116, 59–69.
Gu, C., Wang, F., Zhao, Z., Wang, H., Cong, X., Chen, X., 2017. Lysophosphatidic acid is associated with atherosclerotic plaque instability by regulating NF-KB dependent matrix metalloproteinase-9 expression via lPA2 in macrophages. Front. Physiol. 8, 1–11.
Gu, L., Okada, Y., Clinton, S.K., Gerard, C., Sukhova, G.K., Libby, P., Rollins, B.J., 1998. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor–deficient mice. Mol. Cell. 2, 275–281.
Guenther, P., Bowman, S., Goldman, J., 2013. Alcoholic Beverage Consumption by Adults 21 Years and over in the United States: Results from the National Health and Nutrition Examination Survey, 2003-2006.
Gugliucci, A., 2008. Antithrombin activity is inhibited by acrolein and homocysteine thiolactone: protection by cysteine. Life Sci. 82, 413–418.
Guth, S., Habermeyer, M., Baum, M., Steinberg, P., Lampen, A., Eisenbrand, G., 2013. Thermally induced process-related contaminants: the example of acrolein and the comparison with acrylamide: opinion of the Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG). Mol. Nutr. Food Res. 57, 2269–2282.
Haberzettl, P., Vladykovskaya, E., Srivastava, S., Bhatnagar, A., 2009. Role of endoplasmic reticulum stress in acrolein-induced endothelial activation. Toxicol. Appl. Pharmacol. 234, 14–24.
Hansson, G.K., Libby, P., Tabas, I., 2015. Inflammation and plaque vulnerability. J. Intern. Med. 278, 483–493.
Harrington, J.R., 2000. The role of MCP-1 in atherosclerosis. Stem Cell. 18, 65–66.
Hatters, D.M., Peters-Libeu, C.A., Weisgraber, K.H., 2006. Apolipoprotein E structure: insights into function. Trends Biochem. Sci. 31, 445–454.
Haussmann, H.-J., 2012. Use of hazard indices for a theoretical evaluation of cigarette smoke composition. Chem. Res. Toxicol. 25, 794–810.
Henning, R.J., Johnson, G.T., Coyle, J.P., Harbison, R.D., 2017. Acrolein can cause cardiovascular disease: a review. Cardiovasc. Toxicol. 17, 227–236.
Higashi, K., Igarashi, K., Toida, T., 2016. Recent progress in analytical methods for determination of urinary 3-hydroxypropylmercapturic acid, a major metabolite of acrolein. Biol. Pharm. Bull. 39, 915–919.
Horton, N.D., Biswal, S.S., Corrigan, L.L., Bratta, J., Kehrer, J.P., 1999. Acrolein causes inhibitor κB-independent decreases in nuclear factor κB activation in human lung adenocarcinoma (A549) cells. J. Biol. Chem. 274, 9200–9206.
Hristova, M., Spiess, P.C., Kasahara, D.I., Randall, M.J., Deng, B., van der Vliet, A., 2012. The tobacco smoke component, acrolein, suppresses innate macrophage responses by direct alkylation of c-Jun N-terminal kinase. Am. J. Respir. Cell Mol. Biol. 46, 23–33.
Hu, Z., Zhang, J., Guan, A., Gong, H., Yang, M., Zhang, G., Jia, J., Ma, H., Yang, C., Ge, J., Zou, Y., 2013. Granulocyte colony-stimulating factor promotes atherosclerosis in high-fat diet rabbits. Int. J. Mol. Sci. 14, 4805–4816.
Hutzler, C., Paschke, M., Kruschinski, S., Henkler, F., Hahn, J., Luch, A., 2014. Chemical

hazards present in liquids and vapors of electronic cigarettes. Arch. Toxicol. 88, 1295–1308.
Igarashi, K., Kashiwagi, K., 2011. Protein-conjugated acrolein as a biochemical marker of brain infarction. Mol. Nutr. Food Res. 55, 1332–1341.
Igarashi, K., Uemura, T., Kashiwagi, K., 2018. Acrolein: an effective biomarker for tissue damage produced from polyamines. Methods Mol. Biol. 1694, 459–468.
Jacob, T., Ascher, E., Alapat, D., Olevskaia, Y., Hingorani, A., 2005. Activation of p38MAPK signaling cascade in a VSMC injury model: role of p38MAPK inhibitors in limiting VSMC proliferation. Eur. J. Vasc. Endovasc. Surg. 29, 470–478.
Jahani, V., Kavousi, A., Mehri, S., Karimi, G., 2018. Rho kinase, a potential target in the treatment of metabolic syndrome. Biomed. Pharmacother. 106, 1024–1030.
Kachele, M., Monakhova, Y.B., Kuballa, T., Lachenmeier, D.W., 2014. NMR investigation of acrolein stability in hydroalcoholic solution as a foundation for the valid HS-SPME/GC-MS quantification of the unsaturated aldehyde in beverages. Anal. Chim. Acta 820, 112–118.
Kanogawa, Y., Fujiyoshi, M., Nakazato, Y., Watanabe, K., Kurihara, M., Takezawa, A., Uchida, M., Igarashi, K., Suzuki, T., Ariyoshi, N., 2016. Beta-migrating very low-density lipoprotein conjugates with acrolein in high-cholesterol diet-fed rabbits and localizes to atherosclerotic lesions with macrophages. Int. J. Clin. Exp. Pathol. 9, 11149–11158.
Karbasforooshan, H., Karimi, G., 2017. The role of SIRT1 in diabetic cardiomyopathy. Biomed. Pharmacother. 90, 386–392.
Kasahara, D.I., Poynter, M.E., Othman, Z., Hemenway, D., van der Vliet, A., 2008. Acrolein inhalation suppresses lipopolysaccharide-induced inflammatory cytokine production but does not affect acute airways neutrophilia. J. Immunol. 181, 736–745.
Kassem, N.O.F., Kassem, N.O., Liles, S., Zarth, A.T., Jackson, S.R., Daffa, R.M., Chatfield, D.A., Carmella, S.G., Hecht, S.S., Hovell, M.F., 2017. Acrolein exposure in hookah smokers and non-smokers exposed to hookah tobacco Secondhand Smoke: implications for regulating hookah tobacco products. Nicotine Tob. Res. : Off. J. Soc. Res. Nicotine Tob.
Kautiainen, A., Tornqvist, M., Svensson, K., Osterman-Golkar, S., 1989. Adducts of malonaldehyde and a few other aldehydes to hemoglobin. Carcinogenesis 10, 2123–2130.
Kaye, C.M., 1973. Biosynthesis of mercapturic acids from allyl alcohol, allyl esters and acrolein. Biochem. J. 134, 1093–1101.
Kecili, R., Nivhede, D., Billing, J., Leeman, M., Sellergren, B., Yilmaz, E., 2012. Removal of acrolein from active pharmaceutical ingredients using aldehyde scavengers. Org. Process Res. Dev. 16, 1225–1229.
Kelley, D.E., Boynton, M.H., Noar, S.M., Morgan, J.C., Mendel, J.R., Ribisl, K.M., Stepanov, I., Nylander-French, L.A., Brewer, N.T., 2017. Effective message elements for disclosures about chemicals in cigarette smoke. Nicotine & tobacco research. Off. J. Soc. Res. Nicotine Tob (in press).
Khlystov, A., Samburova, V., 2016. Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping. Environ. Sci. Technol. 50, 13080–13085.
Kim, C.E., Lee, S.J., Seo, K.W., Park, H.M., Yun, J.W., Bae, J.U., Bae, S.S., Kim, C.D., 2010. Acrolein increases 5-lipoxygenase expression in murine macrophages through activation of ERK pathway. Toxicol. Appl. Pharmacol. 245, 76–82.
Kim, J.M., Lee, J.Y., Yoon, Y.M., Oh, Y.K., Youn, J., Kim, Y.J., 2006. NF-κB activation pathway is essential for the chemokine expression in intestinal epithelial cells stimulated with Clostridium difficile toxin A. Scand. J. Immunol. 63, 453–460.
Kirkham, P.A., Spooner, G., Ffoulkes-Jones, C., Calvez, R., 2003. Cigarette smoke triggers macrophage adhesion and activation: role of lipid peroxidation products and scavenger receptor. Free Radic. Biol. Med. 35, 697–710.
Kirsch, J., Schneider, H., Pagel, J.-I., Rehberg, M., Singer, M., Hellfritsch, J., Chillo, O., Schubert, K.M., Qiu, J., Pogoda, K., Kameritsch, P., Uhl, B., Pircher, J., Deindl, E., Müller, S., Kirchner, T., Pohl, U., Conrad, M., Beck, H., 2016. Endothelial dysfunction, and a prothrombotic, proinflammatory phenotype is caused by loss of mitochondrial thioredoxin reductase in endothelium. Arterioscler. Thromb. Vasc. Biol. 36, 1891.
Kobayashi, N., Takano, M., Hata, N., Kume, N., Tsurumi, M., Shirakabe, A., Okazaki, H., Shibuya, J., Shiomura, R., Nishigoori, S., Seino, Y., Shimizu, W., 2016. Matrix metalloproteinase-9 as a marker for plaque rupture and a predictor of adverse clinical outcome in patients with acute coronary syndrome: an optical coherence tomography study. Cardiology 135, 56–65.
Kockx, M.M., Herman, A.G., 2000. Apoptosis in atherosclerosis: beneficial or detrimental? Cardiovasc. Res. 45, 736–746.
Kunjathoor, V.V., Febbraio, M., Podrez, E.A., Moore, K.J., Andersson, L., Koehn, S., Rhee, J.S., Silverstein, R., Hoff, H.F., Freeman, M.W., 2002. Scavenger receptors class A-I/II and CD36 are the principal receptors responsible for the uptake of modified low density lipoprotein leading to lipid loading in macrophages. J. Biol. Chem. 277, 49982–49988.
Lafont, A., 2003. Basic aspects of plaque vulnerability. Heart 89, 1262–1267.
Lambert, C., McCue, J., Portas, M., Ouyang, Y., Li, J., Rosano, T.G., Lazis, A., Freed, B.M., 2005. Acrolein in cigarette smoke inhibits T-cell responses. J. Allergy Clin. Immunol. 116, 916–922.
Laugesen, M., 2015. Nicotine and toxicant yield ratings of electronic cigarette brands in New Zealand. N. Z. Med. J. 128, 77–82.
Lee, M.H., Szulejko, J.E., Kim, K.H., 2018. Determination of carbonyl compounds in electronic cigarette refill solutions and aerosols through liquid-phase dinitrophenyl hydrazine derivatization. Environ. Monit. Assess. 190, 200.
Lemaître, V., Dabo, A.J., D'Armiento, J., 2011. Cigarette smoke components induce matrix metalloproteinase-1 in aortic endothelial cells through inhibition of mTOR signaling. Toxicol. Sci. 123, 542–549.
Ley, K., Miller, Y.I., Hedrick, C.C., 2011. Monocyte and macrophage dynamics during atherogenesis. Arterioscler. Thromb. Vasc. Biol. 31, 1506–1516.
Li, H., Wang, J., Kaphalia, B., Ansari, G.A., Khan, M.F., 2004. Quantitation of acrolein-protein adducts: potential biomarker of acrolein exposure. J. Toxicol. Environ. Health 67, 513–524.
Libby, P., Ridker, P.M., Hansson, G.K., 2011. Progress and challenges in translating the biology of atherosclerosis. Nature 473, 317–325.
Libby, P., Ridker, P.M., Maseri, A., 2002. Inflammation and atherosclerosis. Circulation 105, 1135–1143.
Liu, C.-C., Kanekiyo, T., Xu, H., Bu, G., 2013. Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. Nat. Rev. Neurol. 9, 106–118.
Liuzzo, G., Santamaria, M., Biasucci, L.M., Narducci, M., Colafrancesco, V., Porto, A., Brugaletta, S., Pinnelli, M., Rizzello, V., Maseri, A., Crea, F., 2007. Persistent activation of nuclear factor kappa-B signaling pathway in patients with unstable Angina and elevated levels of C-reactive protein. J. Am. Coll. Cardiol. 49, 185–194.
Lloyd-Jones, D., Adams, R.J., Brown, T.M., Carnethon, M., Dai, S., De Simone, G., Ferguson, T.B., Ford, E., Furie, K., Gillespie, C., Go, A., Greenlund, K., Haase, N., Hailpern, S., Ho, P.M., Howard, V., Kissela, B., Kittner, S., Lackland, D., Lisabeth, L., Marelli, A., McDermott, M.M., Meigs, J., Mozaffarian, D., Mussolino, M., Nichol, G., Roger, V.L., Rosamond, W., Sacco, R., Sorlie, P., Stafford, R., Thom, T., Wasserthiel-Smoller, S., Wong, N.D., Wylie-Rosett, J., 2010. Heart disease and stroke statistics—2010 update a report from the American heart association. Circulation 121, e46–e215.
Louis, S.F., Zahradka, P., 2010. Vascular smooth muscle cell motility: from migration to invasion. Exp. Clin. Cardiol. 15, e75–e85.
Lovell, M.A., Xie, C., Markesbery, W.R., 2000. Acrolein, a product of lipid peroxidation, inhibits glucose and glutamate uptake in primary neuronal cultures. Free Radic. Biol. Med. 29, 714–720.
Lukasz, G.M., Jakub, K., Michal, G., Leon, K., Andrzej, S., Jolanta, K., Adam, P., Magdalena, J.-C., Czeslawa, R.-D., Christopher, H., Peyton, J., Neal, B., 2014. Levels of selected carcinogens and toxicants in vapor from electronic cigarettes. Tobac. Contr. 23, 133–139.
Maier, W., Altwegg, L.A., Corti, R., Gay, S., Hersberger, M., Maly, F.E., Sütsch, G., Roffi, M., Neidhart, M., Eberli, F.R., Tanner, F.C., Gobbi, S., von Eckardstein, A., Lüscher, T.F., 2005. Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein. Circulation 111, 1355–1361.
Mason, D.P., Kenagy, R.D., Hasenstab, D., Bowen-Pope, D.F., Seifert, R.A., Coats, S., Hawkins, S.M., Clowes, A.W., 1999. Matrix metalloproteinase-9 overexpression enhances vascular smooth muscle cell migration and alters remodeling in the injured rat carotid artery. Circ. Res. 85, 1179–1185.
McLaren, J.E., Michael, D.R., Ashlin, T.G., Ramji, D.P., 2011. Cytokines, macrophage lipid metabolism and foam cells: implications for cardiovascular disease therapy. Prog. Lipid Res. 50, 331–347.
McRobbie, H., Phillips, A., Goniewicz, M.L., Smith, K.M., Knight-West, O., Przulj, D., Hajek, P., 2015. Effects of switching to electronic cigarettes with and without concurrent smoking on exposure to nicotine, carbon monoxide, and acrolein. Cancer Prev. Res. 8, 873–878.
Milton, S., Mathew, O., Ranganna, K., Yousefipour, Z., Newaz, M., 2015. Acrolein-induced Vascular Smooth Muscle Cells (VSMC) Cytotoxicity: Differential Effects of N-Acetylcysteine and Ebselen.
Mirkes, P.E., 1985. Cyclophosphamide teratogenesis: a review. Teratog. Carcinog. Mutagen. 5, 75–88.
Moghe, A., Ghare, S., Lamoreau, B., Mohammad, M., Barve, S., McClain, C., Joshi-Barve, S., 2015. Molecular mechanisms of acrolein toxicity: relevance to human disease. Toxicol. Sci. 143, 242–255.
Moon, K.-Y., 2011. Acrolein, an I-κBα-independent downregulator of NF-κB activity, causes the decrease in nitric oxide production in human malignant keratinocytes. Arch. Toxicol. 85, 499–504.
Moore, Kathryn J., Tabas, I., 2011. Macrophages in the pathogenesis of atherosclerosis. Cell 145, 341–355.
Morabito, J.A., Holman, M.R., Ding, Y.S., Yan, X., Chan, M., Chafin, D., Perez, J., Mendez, M.I., Cardenas, R.B., Watson, C., 2017. The use of charcoal in modified cigarette filters for mainstream smoke carbonyl reduction. Regul. Toxicol. Pharmacol. 86, 117–127.
Moreno, P.R., Falk, E., Palacios, I.F., Newell, J.B., Fuster, V., Fallon, J.T., 1994. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 90, 775–778.
Moretto, N., Bertolini, S., Iadicicco, C., Marchini, G., Kaur, M., Volpi, G., Patacchini, R., Singh, D., Facchinetti, F., 2012. Cigarette smoke and its component acrolein augment IL-8/CXCL8 mRNA stability via p38 MAPK/MK2 signaling in human pulmonary cells. Am. J. Physiol. Lung Cell Mol. Physiol. 303, L929–L938.
Morris, J.B., 1996. Uptake of acrolein in the upper respiratory tract of the f344 rat. Inhal. Toxicol. 8, 387–403.
Morris, J.B., Symanowicz, P.T., Olsen, J.E., Thrall, R.S., Cloutier, M.M., Hubbard, A.K., 2003. Immediate sensory nerve-mediated respiratory responses to irritants in healthy and allergic airway-diseased mice. J. Appl. Physiol. 94, 1563–1571 Bethesda, Md. : 1985.
Myers, C.R., Myers, J.M., 2009. The effects of acrolein on peroxiredoxins, thioredoxins, and thioredoxin reductase in human bronchial epithelial cells. Toxicology 257, 95–104.
Myers, C.R., Myers, J.M., Kufahl, T.D., Forbes, R., Szadkowski, A., 2011. The effects of acrolein on the thioredoxin system: implications for redox-sensitive signaling. Mol. Nutr. Food Res. 55, 1361–1374.
Naghavi, M., Libby, P., Falk, E., Casscells, S.W., Litovsky, S., Rumberger, J., Badimon, J.J., Stefanadis, C., Moreno, P., Pasterkamp, G., Fayad, Z., Stone, P.H., Waxman, S., Raggi, P., Madjid, M., Zarrabi, A., Burke, A., Yuan, C., Fitzgerald, P.J., Siscovick, D.S., de Korte, C.L., Aikawa, M., Juhani Airaksinen, K.E., Assmann, G., Becker, C.R., Chesebro, J.H., Farb, A., Galis, Z.S., Jackson, C., Jang, I.-K., Koenig, W., Lodder, R.A.,

March, K., Demirovic, J., Navab, M., Priori, S.G., Rekhter, M.D., Bahr, R., Grundy, S.M., Mehran, R., Colombo, A., Boerwinkle, E., Ballantyne, C., Insull, W., Schwartz, R.S., Vogel, R., Serruys, P.W., Hansson, G.K., Faxon, D.P., Kaul, S., Drexler, H., Greenland, P., Muller, J.E., Virmani, R., Ridker, P.M., Zipes, D.P., Shah, P.K., Willerson, J.T., 2003. From vulnerable plaque to vulnerable patient A call for new definitions and risk assessment strategies: Part I. Circulation 108, 1664–1672.
Nakamura, M., Uemura, T., Saiki, R., Sakamoto, A., Park, H., Nishimura, K., Terui, Y., Toida, T., Kashiwagi, K., Igarashi, K., 2016. Toxic acrolein production due to Ca^{2+} influx by the NMDA receptor during stroke. Atherosclerosis 244, 131–137.
Napetschnig, J., Wu, H., 2013. Molecular basis of NF-KB signaling. Annu. Rev. Biophys. 42, 443–468.
Napoli, C., de Nigris, F., Palinski, W., 2001. Multiple role of reactive oxygen species in the arterial wall. J. Cell. Biochem. 82, 674–682.
Newby, A.C., Zaltsman, A.B., 1999. Fibrous cap formation or destruction–the critical importance of vascular smooth muscle cell proliferation, migration and matrix formation. Cardiovasc. Res. 41, 345–360.
Noerager, B.D., Xu, X., Davis, V.A., Jones, C.W., Okafor, S., Whitehead, A., Blalock, J.E., Jackson, P.L., 2015. A potential role for acrolein in neutrophil-mediated chronic inflammation. Inflammation 38, 2279–2287.
Nother, K., Ashley Madeleine, S., Clayton Peter, M., 2016. Influence of type and amount of carbon in cigarette filters on smokers' mouth level exposure to “tar”, nicotine, 1,3-butadiene, benzene, toluene, isoprene, and acrylonitrile. Beiträge Tabakforsch. Int. Contrib. Tob. Res. 40.
O'Toole, T.E., Conklin, D.J., Bhatnagar, A., 2008. Environmental risk factors for heart disease. Rev. Environ. Health 23, 167–202.
O'Toole, T.E., Zheng, Y.-T., Hellmann, J., Conklin, D.J., Barski, O., Bhatnagar, A., 2009. Acrolein activates matrix metalloproteinases by increasing reactive oxygen species in macrophages. Toxicol. Appl. Pharmacol. 236, 194–201.
Ogunwale, M.A., Li, M., Ramakrishnam Raju, M.V., Chen, Y., Nantz, M.H., Conklin, D.J., Fu, X.-A., 2017. Aldehyde detection in electronic cigarette aerosols. ACS Omega 2, 1207–1214.
Ohman, M.K., Wright, A.P., Wickenheiser, K.J., Luo, W., Russo, H.M., Eitzman, D.T., 2010. Monocyte chemoattractant protein-1 deficiency protects against visceral fat-induced atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 30, 1151–1158.
Osório, V.M., de Lourdes Cardeal, Z., 2011. Determination of acrolein in French fries by solid-phase microextraction gas chromatography and mass spectrometry. J. Chromatogr. A 1218, 3332–3336.
Osório, V.M., de Lourdes Cardeal, Z., 2013a. Using SPME-GC/MS to evaluate acrolein production in cassava and pork sausage fried in different vegetable oils. J. Am. Oil Chem. Soc. 90, 1795–1800.
Osório, V.M., de Lourdes Cardeal, Z., 2013b. Using SPME-GC/MS to evaluate acrolein production in cassava and pork sausage fried in different vegetable oils. J. Am. Oil Chem. Soc. 90, 1795–1800.
Pang, X., Lewis, A.C., 2011. Carbonyl compounds in gas and particle phases of mainstream cigarette smoke. Sci. Total Environ. 409, 5000–5009.
Parent, R.A., Caravello, H.E., Sharp, D.E., 1996. Metabolism and distribution of [2,3-14C] acrolein in Sprague-Dawley rats. J. Appl. Toxicol. 16, 449–457.
Park, Y.S., Kim, J., Misonou, Y., Takamiya, R., Takahashi, M., Freeman, M.R., Taniguchi, N., 2007. Acrolein induces Cyclooxygenase-2 and prostaglandin production in human umbilical vein endothelial cells Roles of p38 MAP Kinase. Arterioscler. Thromb. Vasc. Biol. 27, 1319–1325.
Park, Y.S., Misonou, Y., Fujiwara, N., Takahashi, M., Miyamoto, Y., Koh, Y.H., Suzuki, K., Taniguchi, N., 2005. Induction of thioredoxin reductase as an adaptive response to acrolein in human umbilical vein endothelial cells. Biochem. Biophys. Res. Commun. 327, 1058–1065.
Park, Y.S., Taniguchi, N., 2008. Acrolein induces inflammatory response underlying endothelial dysfunction: a risk factor for atherosclerosis. Ann. N. Y. Acad. Sci. 1126, 185–189.
Patel, J.M., Block, E.R., 1993. Acrolein-induced injury to cultured pulmonary artery endothelial cells. Toxicol. Appl. Pharmacol. 122, 46–53.
Patel, J.M., Wood, J.C., Leibman, K.C., 1980. The biotransformation of allyl alcohol and acrolein in rat liver and lung preparations. Drug Metab. Dispos. 8, 305–308.
Perez, C.M., Ledbetter, A.D., Hazari, M.S., Haykal-Coates, N., Carll, A.P., Winsett, D.W., Costa, D.L., Farraj, A.K., 2013. Hypoxia stress test reveals exaggerated cardiovascular effects in hypertensive rats after exposure to the air pollutant acrolein. Toxicol. Sci. 132, 467–477.
Piadé, J.J., Wajrock, S., Jaccard, G., Janeke, G., 2013. Formation of mainstream cigarette smoke constituents prioritized by the World Health Organization – yield patterns observed in market surveys, clustering and inverse correlations. Food Chem. Toxicol. 55, 329–347.
Plana, N., Ibarretxe, D., Cabre, A., Ruiz, E., Masana, L., 2014. Prevalence of atherogenic dyslipidemia in primary care patients at moderate-very high risk of cardiovascular disease. Cardiovascular risk perception. Clín. Invest. Arterioscler. 26, 274–284.
Plutzky, J., 2003. The vascular biology of atherosclerosis. Am. J. Med. 115, 55–61.
Polzin, G.M., Zhang, L., Hearn, B.A., Tavakoli, A.D., Vaughan, C., Ding, Y.S., Ashley, D.L., Watson, C.H., 2008. Effect of charcoal-containing cigarette filters on gas phase volatile organic compounds in mainstream cigarette smoke. Tobac. Contr. 17, i10–i16.
Ranganna, K., Mathew, O.P., Yatsu, F.M., Yousefipour, Z., Hayes, B.E., Milton, S.G., 2007. Involvement of glutathione/glutathione S-transferase antioxidant system in butyrate-inhibited vascular smooth muscle cell proliferation. FEBS J. 274, 5962–5978.
Ranganna, K., Yousefipour, Z., Nasif, R., Yatsu, F.M., Milton, S.G., Hayes, B.E., 2002. Acrolein activates mitogen-activated protein kinase signal transduction pathways in rat vascular smooth muscle cells. Mol. Cell. Biochem. 240, 83–98.
Registry, A.f.T.S.a.D., 2007. Toxicological Profile for Acrolein. US Department of Health and Human Services, Public Health Service, Atlanta, GA.
Rempher, K.J., 2006. Cardiovascular sequelae of tobacco smoking. Crit. Care Nurs. Clin. 18, 13–20.
Rensen, S.S.M., Doevendans, P., van Eys, G., 2007. Regulation and characteristics of vascular smooth muscle cell phenotypic diversity. Neth. Heart J. 15, 100–108.
Roemer, E., Stabbert, R., Rustemeier, K., Veltel, D.J., Meisgen, T.J., Reininghaus, W., Carchman, R.A., Gaworski, C.L., Podraza, K.F., 2004. Chemical composition, cytotoxicity and mutagenicity of smoke from US commercial and reference cigarettes smoked under two sets of machine smoking conditions. Toxicology 195, 31–52.
Rom, O., Korach-Rechtman, H., Hayek, T., Danin-Poleg, Y., Bar, H., Kashi, Y., Aviram, M., 2017. Acrolein increases macrophage atherogenicity in association with gut microbiota remodeling in atherosclerotic mice: protective role for the polyphenol-rich pomegranate juice. Arch. Toxicol. 91, 1709–1725.
Saiki, R., Hayashi, D., Ikuo, Y., Nishimura, K., Ishii, I., Kobayashi, K., Chiba, K., Toida, T., Kashiwagi, K., Igarashi, K., 2013. Acrolein stimulates the synthesis of IL-6 and C-reactive protein (CRP) in thrombosis model mice and cultured cells. J. Neurochem. 127, 652–659.
Saiki, R., Nishimura, K., Ishii, I., Omura, T., Okuyama, S., Kashiwagi, K., Igarashi, K., 2009. Intense correlation between brain infarction and protein-conjugated acrolein. Stroke 40, 3356–3361.
Saiki, R., Park, H., Ishii, I., Yoshida, M., Nishimura, K., Toida, T., Tatsukawa, H., Kojima, S., Ikeguchi, Y., Pegg, A.E., 2011. Brain infarction correlates more closely with acrolein than with reactive oxygen species. Biochem. Biophys. Res. Commun. 404, 1044–1049.
Saitoh, M., Nishitoh, H., Fujii, M., Takeda, K., Tobiume, K., Sawada, Y., Kawabata, M., Miyazono, K., Ichijo, H., 1998. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. EMBO J. 17, 2596–2606.
Seaman, V.Y., Bennett, D.H., Cahill, T.M., 2009. Indoor acrolein emission and decay rates resulting from domestic cooking events. Atmos. Environ. 43, 6199–6204.
Shah, P.K., 2007. Molecular mechanisms of plaque instability. Curr. Opin. Lipidol. 18, 492–499.
Shao, B.-z., Han, B.-z., Zeng, Y.-x., Su, D.-f., Liu, C., 2016. The roles of macrophage autophagy in atherosclerosis. Acta Pharmacol. Sin. 37, 150–156.
Shao, B., Fu, X., McDonald, T.O., Green, P.S., Uchida, K., O'Brien, K.D., Oram, J.F., Heinecke, J.W., 2005. Acrolein Impairs ATP binding cassette transporter A1-dependent cholesterol export from cells through site-specific modification of Apolipoprotein A-I. J. Biol. Chem. 280, 36386–36396.
Sithu, S.D., Srivastava, S., Siddiqui, M.A., Vladykovskaya, E., Riggs, D.W., Conklin, D.J., Haberzettl, P., O'Toole, T.E., Bhatnagar, A., D'Souza, S.E., 2010. Exposure to acrolein by inhalation causes platelet activation. Toxicol. Appl. Pharmacol. 248, 100–110.
Sleiman, M., Logue, J.M., Montesinos, V.N., Russell, M.L., Litter, M.I., Gundel, L.A., Destaillats, H., 2016. Emissions from electronic cigarettes: key parameters affecting the release of harmful chemicals. Environ. Sci. Technol. 50, 9644–9651.
Song, J., Cho, K.J., Cheon, S.Y., Kim, S.-H., Park, K.A., Lee, W.T., Lee, J.E., 2013a. Apoptosis signal-regulating kinase 1 (ASK1) is linked to neural stem cell differentiation after ischemic brain injury. Exp. Mol. Med. 45, e69.
Song, J.J., Lee, J.D., Lee, B.D., Chae, S.W., Park, M.K., 2013b. Effect of acrolein, a hazardous air pollutant in smoke, on human middle ear epithelial cells. Int. J. Pediatr. Otorhinolaryngol. 77, 1659–1664.
Srivastava, S., Sithu, S.D., Vladykovskaya, E., Haberzettl, P., Hoetker, D.J., Siddiqui, M.A., Conklin, D.J., D'Souza, S.E., Bhatnagar, A., 2011. Oral exposure to acrolein exacerbates atherosclerosis in apoE-null mice. Atherosclerosis 215, 301–308.
Starke, R.M., Ali, M.S., Jabbour, P.M., Tjoumakaris, S.I., Gonzalez, F., Hasan, D.M., Rosenwasser, R.H., Owens, G.K., Koch, W.J., Dumont, A.S., 2013. Cigarette smoke modulates vascular smooth muscle phenotype: implications for carotid and cerebrovascular disease. PLoS One 8, e71954.
Stefanadis, C., Antoniou, C.K., Tsiachris, D., Pietri, P., 2017. Coronary atherosclerotic vulnerable plaque: current perspectives. J. Am. Heart Assoc. 6, e005543.
Steiner, S., Bisig, C., Petri-Fink, A., Rothen-Rutishauser, B., 2016. Diesel exhaust: current knowledge of adverse effects and underlying cellular mechanisms. Arch. Toxicol. 90, 1541–1553.
Stevens, J.F., Maier, C.S., 2008. Acrolein: sources, metabolism, and biomolecular interactions relevant to human health and disease. Mol. Nutr. Food Res. 52, 7–25.
Su, B., Mitra, S., Gregg, H., Flavahan, S., Chotani, M.A., Clark, K.R., Goldschmidt-Clermont, P.J., Flavahan, N.A., 2001. Redox regulation of vascular smooth muscle cell differentiation. Circ. Res. 89, 39–46.
Sun, L., Luo, C., Long, J., Wei, D., Liu, J., 2006. Acrolein is a mitochondrial toxin: effects on respiratory function and enzyme activities in isolated rat liver mitochondria. Mitochondrion 6, 136–142.
Sun, Y., Ito, S., Nishio, N., Tanaka, Y., Chen, N., Isobe, K.-i., 2014. Acrolein induced both pulmonary inflammation and the death of lung epithelial cells. Toxicol. Lett. 229, 384–392.
Swystun, L., Mukherjee, S., Levine, M., Liaw, P., 2011. The chemotherapy metabolite acrolein upregulates thrombin generation and impairs the protein C anticoagulant pathway in animal-based and cell-based models. J. Thromb. Haemost. 9, 767–775.
Szadkowski, A., Myers, C.R., 2008. Acrolein oxidizes the cytosolic and mitochondrial thioredoxins in human endothelial cells. Toxicology 243, 164–176.
Taghiabadi, E., Imenshahidi, M., Abnous, K., Mosafa, F., Sankian, M., Memar, B., Karimi, G., 2012. Protective effect of silymarin against acrolein-induced cardiotoxicity in mice. Evid. Based Complement. Alternat. Med. 1–14.
Talih, S., Balhas, Z., Salman, R., Karaoghlanian, N., Shihadeh, A., 2016. Direct dripping": a high-temperature, high-formaldehyde emission electronic cigarette use method. Nicotine & tobacco research. Off. J. Soc. Res. Nicotine Tob. 18, 453–459.
Talih, S., Salman, R., Karaoghlanian, N., El-Hellani, A., Saliba, N., Eissenberg, T., Shihadeh, A., 2017. Juice Monsters": sub-ohm vaping and toxic volatile aldehyde emissions. Chem. Res. Toxicol. 30, 1791–1793.
Tamamizu-Kato, S., Wong, J.Y., Jairam, V., Uchida, K., Raussens, V., Kato, H., Ruysschaert, J.-M., Narayanaswami, V., 2007. Modification by acrolein, a component

of tobacco smoke and age-related oxidative stress, mediates functional impairment of human apolipoprotein. E. Biochem. 46, 8392–8400.
Tang, M.S., Wang, H.T., Hu, Y., Chen, W.S., Akao, M., Feng, Z., Hu, W., 2011. Acrolein induced DNA damage, mutagenicity and effect on DNA repair. Mol. Nutr. Food Res. 55, 1291–1300.
Tayyarah, R., Long, G.A., 2014. Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. Regul. Toxicol. Pharmacol. 70, 704–710.
Tian, R., Shi, R., 2017. Dimercaprol is an acrolein scavenger that mitigates acrolein-mediated PC-12 cells toxicity and reduces acrolein in rat following spinal cord injury. J. Neurochem. 141, 708–720.
Togashi, M., Terai, T., Kojima, H., Hanaoka, K., Igarashi, K., Hirata, Y., Urano, Y., Nagano, T., 2014. Practical fluorescence detection of acrolein in human plasma via a two-step tethering approach. Chem. Commun. 50, 14946–14948.
Togashi, M., Urano, Y., Kojima, H., Terai, T., Hanaoka, K., Igarashi, K., Hirata, Y., Nagano, T., 2010. Sensitive detection of acrolein in serum using time-resolved Luminescence. Org. Lett. 12, 1704–1707.
Tomitori, H., Usui, T., Saeki, N., Ueda, S., Kase, H., Nishimura, K., Kashiwagi, K., Igarashi, K., 2005. Polyamine oxidase and acrolein as novel biochemical markers for diagnosis of cerebral stroke. Stroke 36, 2609–2613.
Tran, T.N., Kosaraju, M.G., Tamamizu-Kato, S., Akintunde, O., Zheng, Y., Bielicki, J.K., Pinkerton, K., Uchida, K., Lee, Y.Y., Narayanaswami, V., 2014. Acrolein modification impairs key functional features of rat apolipoprotein E: identification of modified sites by mass spectrometry. Biochemistry 53, 361–375.
Uchida, K., Kanematsu, M., Morimitsu, Y., Osawa, T., Noguchi, N., Niki, E., 1998. Acrolein is a product of lipid peroxidation reaction: formation of free acrolein and its conjugate with lysine residues in oxidized low density lipoproteins. J. Biol. Chem. 273, 16058–16066.
Uchiyama, S., Hayashida, H., Izu, R., Inaba, Y., Nakagome, H., Kunugita, N., 2015. Determination of nicotine, tar, volatile organic compounds and carbonyls in mainstream cigarette smoke using a glass filter and a sorbent cartridge followed by the two-phase/one-pot elution method with carbon disulfide and methanol. J. Chromatogr. A 1426, 48–55.
Uchiyama, S., Senoo, Y., Hayashida, H., Inaba, Y., Nakagome, H., Kunugita, N., 2016. Determination of chemical compounds generated from second-generation e-cigarettes using a sorbent cartridge followed by a two-step elution method. Anal. Sci. 32, 549–555.
Uemura, T., Suzuki, T., Saiki, R., Dohmae, N., Ito, S., Takahashi, H., Toida, T., Kashiwagi, K., Igarashi, K., 2017. Activation of MMP-9 activity by acrolein in saliva from patients with primary Sjogren's syndrome and its mechanism. Int. J. Biochem. Cell Biol. 88, 84–91.
Vacek, T.P., Rehman, S., Neamtu, D., Yu, S., Givimani, S., Tyagi, S.C., 2015. Matrix metalloproteinases in atherosclerosis: role of nitric oxide, hydrogen sulfide, homocysteine, and polymorphisms. Vasc. Health Risk Manag. 11, 173–183.
Valacchi, G., Pagnin, E., Phung, A., Nardini, M., Schock, B.C., Cross, C.E., Van Der Vliet, A., 2004. Inhibition of NFκB activation and IL-8 expression in human bronchial epithelial cells by acrolein. Antioxidants Redox Signal. 7, 25–31.
Valko, M., Jomova, K., Rhodes, C.J., Kuča, K., Musílek, K., 2016. Redox- and non-redox-metal-induced formation of free radicals and their role in human disease. Arch. Toxicol. 90, 1–37.
van der Wal, A.C., Becker, A.E., van der Loos, C.M., Das, P.K., 1994. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 89, 36–44.
Viles-Gonzalez, J.F., Fuster, V., Badimon, J.J., 2004. Atherothrombosis: a widespread disease with unpredictable and life-threatening consequences. Eur. Heart J. 25, 1197–1207.
Vreeke, S., Peyton, D.H., Strongin, R.M., 2018. Triacetin enhances levels of acrolein, formaldehyde hemiacetals, and acetaldehyde in electronic cigarette aerosols. ACS Omega 3, 7165–7170.
Wang, G.W., Guo, Y., Vondriska, T.M., Zhang, J., Zhang, S., Tsai, L.L., Zong, N.C., Bolli, R., Bhatnagar, A., Prabhu, S.D., 2008. Acrolein consumption exacerbates myocardial ischemic injury and blocks nitric oxide-induced PKCepsilon signaling and cardioprotection. J. Mol. Cell. Cardiol. 44, 1016–1022.
Wang, H.T., Hu, Y., Tong, D., Huang, J., Gu, L., Wu, X.R., Chung, F.L., Li, G.M., Tang, M.S., 2012. Effect of carcinogenic acrolein on DNA repair and mutagenic susceptibility. J. Biol. Chem. 287, 12379–12386.
Watanabe, K., Nakazato, Y., Saiki, R., Igarashi, K., Kitada, M., Ishii, I., 2013. Acrolein-conjugated low-density lipoprotein induces macrophage foam cell formation. Atherosclerosis 227, 51–57.
Wheat, L.A., Haberzettl, P., Hellmann, J., Baba, S.P., Bertke, M., Lee, J., McCracken, J., O'Toole, T.E., Bhatnagar, A., Conklin, D.J., 2011. Acrolein inhalation prevents VEGF-induced mobilization of Flk-1(+)/Sca-1(+) cells in mice. Arterioscler. Thromb. Vasc. Biol. 31, 1598–1606.
Wilson, S.H., Caplice, N.M., Simari, R.D., Holmes, D.R., Carlson, P.J., Lerman, A., 2000. Activated nuclear factor-κB is present in the coronary vasculature in experimental hypercholesterolemia. Atherosclerosis 148, 23–30.
Woodruff, T.J., Wells, E.M., Holt, E.W., Burgin, D.E., Axelrad, D.A., 2007. Estimating risk from ambient concentrations of acrolein across the United States. Environ. Health Perspect. 115, 410–415.
Xu, C.B., Lei, Y., Chen, Q., Pehrson, C., Larsson, L., Edvinsson, L., 2010. Cigarette smoke extracts promote vascular smooth muscle cell proliferation and enhances contractile responses in the vasculature and airway. Basic Clin. Pharmacol. Toxicol. 107, 940–948.
Xu, F., Sun, Y., Chen, Y., Sun, Y., Li, R., Liu, C., Zhang, C., Wang, R., Zhang, Y., 2009. Endothelial cell apoptosis is responsible for the formation of coronary thrombotic atherosclerotic plaques. Tohoku J. Exp. Med. 218, 25–33.
Yabluchanskiy, A., Ma, Y., Iyer, R.P., Hall, M.E., Lindsey, M.L., 2013. Matrix metalloproteinase-9: many shades of function in cardiovascular disease. Physiology 28, 391–403.
Yadav, U.C.S., Ramana, K.V., 2013. Regulation of NF-B-induced inflammatory signaling by lipid peroxidation-derived aldehydes. Oxid. Med. Cell. Longev. 2013, 1–11.
Yasuhara, A., Shibamoto, T., 1991. Determination of acrolein evolved from heated vegetable oil by N-methylhydrazine conversion. Agric. Biol. Chem. 55, 2639–2640.
Yoshida, H., Kisugi, R., 2010. Mechanisms of LDL oxidation. Clin. Chim. Acta 411, 1875–1882.
Yoshida, M., Higashi, K., Kobayashi, E., Saeki, N., Wakui, K., Kusaka, T., Takizawa, H., Kashiwado, K., Suzuki, N., Fukuda, K., Nakamura, T., Watanabe, S., Tada, K., Machi, Y., Mizoi, M., Toida, T., Kanzaki, T., Tomitori, H., Kashiwagi, K., Igarashi, K., 2010. Correlation between images of silent brain infarction, carotid atherosclerosis and white matter hyperintensity, and plasma levels of acrolein, IL-6 and CRP. Atherosclerosis 211, 475–479.
Yoshida, M., Tomitori, H., Machi, Y., Hagihara, M., Higashi, K., Goda, H., Ohya, T., Niitsu, M., Kashiwagi, K., Igarashi, K., 2009a. Acrolein toxicity: comparison with reactive oxygen species. Biochem. Biophys. Res. Commun. 378, 313–318.
Yoshida, M., Tomitori, H., Machi, Y., Katagiri, D., Ueda, S., Horiguchi, K., Kobayashi, E., Saeki, N., Nishimura, K., Ishii, I., Kashiwagi, K., Igarashi, K., 2009b. Acrolein, IL-6 and CRP as markers of silent brain infarction. Atherosclerosis 203, 557–562.
Yoshiyama, S., Horinouchi, T., Miwa, S., Wang, H.H., Kohama, K., Nakamura, A., 2011. Effect of cigarette smoke components on vascular smooth muscle cell migration toward platelet-derived growth factor BB. J. Pharmacol. Sci. 115, 532–535.
Yousefian, M., Shakour, N., Hosseinzadeh, H., Hayes, A.W., Hadizadeh, F., Karimi, G., 2018. The natural phenolic compounds as modulators of NADPH oxidases in hypertension. Phytomedicine 55, 200–213.
Yousefipour, Z., Chug, N., Marek, K., Nesbary, A., Mathew, J., Ranganna, K., Newaz, M.A., 2017. Contribution of PPARgamma in modulation of acrolein-induced inflammatory signaling in gp91phox knock-out mice. Biochem. Cell Biol. 95, 482–490.
Yousefipour, Z., Newaz, M.A., 2011. Involvement of serum response factor (SRF) in acrolein-mediated activation of NF[kappa]B in vascular smooth muscle cells (VSMC). FASEB J. 25, 821–824.
Yousefipour, Z., Ranganna, K., Newaz, M.A., Milton, S.G., 2005. Mechanism of acrolein-induced vascular toxicity. J. Physiol. Pharmacol. 56, 337–353.
Yousefipour, Z., Zhang, C., Monfareed, M., Walker, J., Newaz, M., 2013. Acrolein-induced oxidative stress in NAD(P)H Oxidase Subunit gp91phox knock-out mice and its modulation of NFkappaB and CD36. J. Health Care Poor Underserved 24, 118–131.
Zamora, R., Aguilar, I., Granvogl, M., Hidalgo, F.J., 2016. Toxicologically relevant aldehydes produced during the frying process are trapped by food phenolics. J. Agric. Food Chem. 64, 5583–5589.
Zanobetti, A., Schwartz, J., 2009. The effect of fine and coarse particulate air pollution on mortality: a national analysis. Environ. Health Perspect. 117, 898–903.
Zhang, X., Chen, J., Wang, S., 2017. Serum amyloid a induces a vascular smooth muscle cell phenotype switch through the p38 MAPK signaling pathway. BioMed Res. Int. 2017, 1–11.
Zhao, J.-F., Hsiao, S.-H., Hsu, M.-H., Pao, K.-C., Kou, Y.R., Shyue, S.-K., Lee, T.-S., 2016. Di-(2-ethylhexyl) phthalate accelerates atherosclerosis in apolipoprotein E-deficient mice. Arch. Toxicol. 90, 181–190.
Zhao, W., Zhang, Q., Lu, B., Sun, S., Zhang, S., Zhang, J., 2017. Rapid determination of six low molecular carbonyl compounds in tobacco smoke by the apci-ms/ms coupled to data mining. Biochem. J. Anal. Sci. Methods Chem. 2017, 8260860.
Zhu, Q., Sun, Z., Jiang, Y., Chen, F., Wang, M., 2011. Acrolein scavengers: reactivity, mechanism and impact on health. Mol. Nutr. Food Res. 55, 1375–1390.
Zhu, Q., Zheng, Z.P., Cheng, K.W., Wu, J.J., Zhang, S., Tang, Y.S., Sze, K.H., Chen, J., Chen, F., Wang, M., 2009. Natural polyphenols as direct trapping agents of lipid peroxidation-derived acrolein and 4-hydroxy-trans-2-nonenal. Chem. Res. Toxicol. 22, 1721–1727.
Zulueta, A., Caretti, A., Campisi, G.M., Brizzolari, A., Abad, J.L., Paroni, R., Signorelli, P., Ghidoni, R., 2017. Inhibitors of ceramide de novo biosynthesis rescue damages induced by cigarette smoke in airways epithelia. Naunyn-Schmiedeberg's Arch. Pharmacol. 390, 753–759.
Żyżelewicz, D., Oracz, J., Krysiak, W., Budryn, G., Nebesny, E., 2017. Effects of various roasting conditions on acrylamide, acrolein, and polycyclic aromatic hydrocarbons content in cocoa bean and the derived chocolates. Dry. Technol. 35, 363–374.