APPENDIX A6.1.3.23 ACETALDEHYDE - FACTSHEET

	HPHC	BoExp assessed by PMI
IUPAC name	Ethanal	NA
Usual abbreviation	HAc, MeCHO	
Other names	Acetic aldehyde, ethyl aldehyde, aldehyde, acetic ethanol	
CAS number	75-07-0	
Formula and molecular weight	C_2H_4O MW: 44.05	

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Main characteristics

Chemical class	Aldehyde
HPHC lists	FDA-93 [1]; FDA-18 [2]; HC [3, 4]; PMI-58; WHO-39 [5]; WHO-18 [6]; WHO-9 [6]
Source in cigarettes	Amount in main stream smoke (3R4F): 567 µg/cigarette (ISO); 1534 µg/cigarette (HCI) [7] Smoke phase: gas/vapor and particulate phases [8] Presence in tobacco / pyrosynthesis (T°): present in uncombusted tobacco [9] / 25–500 °C [10]. Natural tobacco polysaccharides are the primary precursors of acetaldehyde in tobacco smoke [11], but malic acid is also a precursor of acetaldehyde [12].
Other sources	Occupational exposure to acetaldehyde may occur in its production, in the production of acetic acid, acetate esters and other chemicals and in other applications [13]. Acetaldehyde is a natural product of combustion and photo-oxidation of hydrocarbons commonly found in the atmosphere. It is an important industrial chemical and may be released into the air or in wastewater during its production and use. It has been detected at low levels in drinking-water, surface water, rainwater, effluents, engine exhaust and ambient and indoor air samples. It is also photochemically produced in surface water. Acetaldehyde is an intermediate product in the metabolism of ethanol (Figure 1) and sugars and therefore occurs in trace quantities in human blood. It is present in small amounts in all alcoholic beverages, such as beer, wine and spirits and in plant juices and essential oils, roasted coffee and tobacco smoke [13]. Significant exposures to acetaldehyde can also occur upon alcohol consumption, as it is a major metabolite of alcohol [14, 15].
Toxicity class (FDA) [1]	CA, RT, AD
Toxicity – CA [16]	IARC: group 2B:: possibly carcinogenic to humans [13] IARC group 1: carcinogenic to humans for acetaldehyde associated with consumption of alcoholic beverages [17]. An increased relative frequency of bronchial and oral cavity tumors was found among nine cancer cases in one study of chemical workers exposed to various aldehydes. Esophageal tumors have been associated with genetically determined, high metabolic levels of acetaldehyde after drinking alcohol. It produced tumors of the respiratory tract following inhalation, particularly adenocarcinomas

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	and squamous-cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters.
Toxicity – RT	The irritant effect of acetaldehyde vapor, which is reported to cause coughing and a burning sensation in the nose, throat and eyes, usually prevents exposure to a level sufficient to cause depression of the central nervous system [13]. During inhalation exposure of rats, degeneration of nasal epithelium occurs and leads to hyperplasia and proliferation.
Toxicity – CT	Aldehydes, including acetaldehyde, produce sympathomimetic effects by the release of norepinephrine from adrenergic neurons [18].
Toxicity – RDT	High incidences of fetal resorptions were seen with multiple administrations of acetaldehyde to pregnant mice, and neural tube defects were seen following single IV injections [18].
Toxicity – AD	Direct administration of acetaldehyde, especially into the brain, induces several effects that mimic those of alcohol. High doses of acetaldehyde induce sedative and has movement- and memory-impairing effects, whereas lower doses produce behavioral effects (e.g., stimulation and reinforcement) that are characteristic of addictive drugs. Acetaldehyde is thought to contribute to the addictive properties of tobacco smoke [18, 19].
Toxicity - others	All available toxicity data can be found on the Website Aggregated Computational Toxicology Resource (ACToR) [20].

ADME properties

Absorption [21] - Acetaldehyde is rapidly absorbed by oral and respiratory routes. Estimated half-lives of acetaldehyde in circulating blood have been reported to be very short, i.e. 90 seconds [22].

Distribution [21] - Experimental studies indicate that, following inhalation or oral exposure, sufficient first-pass metabolism occurs in the liver and respiratory tract to limit acetaldehyde access to the systemic circulation [23]. However, acetaldehyde was detectable in the liver, blood, kidney, spleen, heart, and bone of male Sprague-Dawley rats exposed to 1 to 20 mM vapor for 1 hour, which is an extremely high concentration (i.e. 44 to 881 mg acetaldehyde/L air) [24].

Metabolism [21] - Acetaldehyde is metabolized (mainly in mammalian liver) to acetic acid by NAD+-dependent aldehyde dehydrogenase (ADH or ALDH) (Figure 1) [23]. The rate of metabolism to acetic acid varies, but it is generally considered to be rapid. Saturation kinetics are not apparent even with large doses. Acetic acid enters the metabolic pool of intermediary metabolism and is used in the production of carbon dioxide and water or in cellular synthesis of cholesterol, fatty acids, and other tissue constituents [15].

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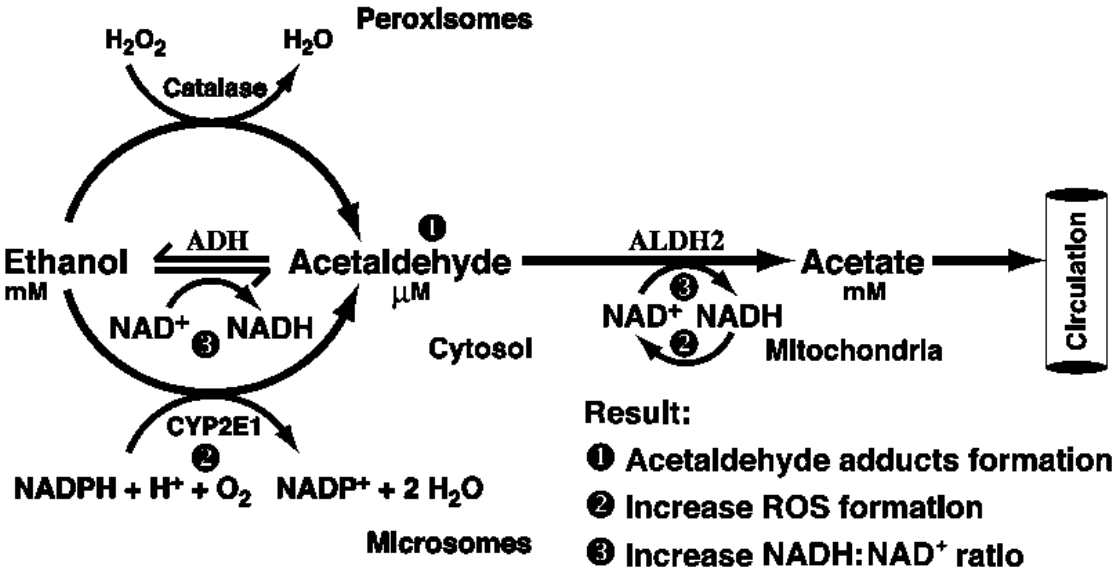


Figure 1. Ethanol metabolism [25]
Alcohol dehydrogenase (ADH), aldehyde dehydrogenase 2 (ALDH2), cytochrome P450 2E1 (CYP2E1), reactive oxygen species (ROS).

Figure source: National Institute on Alcohol Abuse and Alcoholism (NIAAA), Bethesda, Maryland.

In vitro, acetaldehyde formed adducts with cytosine- and purine- containing nucleotides [14]. Similar adducts have been shown *in vivo* in studies on alcohol consumption [26, 27]. Increased adducts were detected in the in leukocyte DNA of alcoholics, as well as in oral cells, in the brain of ethanol-treated mice and in the liver, esophagus, tongue, and submandibular gland DNA of *Aldh2* knockout mice exposed to ethanol [28]. Together with the epidemiological data showing a dramatic increase of risk for esophageal and head and neck cancers in ALDH2-deficient drinkers, the results from the DNA damage studies contributed to the classification of acetaldehyde related to alcohol consumption as carcinogenic to humans (Group 1) by the IARC [17].

Excretion [21] - Because the major metabolite of acetaldehyde enters into intermediary metabolism, the excretion of the parent compound or its metabolites is limited. Acetaldehyde has been detected in expired air, but only its metabolites (N-nitroso-2-methylthiazolidine 4-carboxylic acid; *N*-nitrosothiazolidine 4-carboxylic acid [29]) have been detected in the urine. The precursor 2-methylthiazolidine-4-carboxylic acid (MTCA, a condensation product of acetaldehyde and cysteine) is a more promising BoExp for acetaldehyde [30]. Furthermore, the condensation product of acetaldehyde and cysteinylglycine has also some potential to serve as a BoExp to acetaldehyde [31, 32]. All of these BoExp have the problem of high background levels from other sources, in particular, alcohol consumption.

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Exposure levels in smokers and non-smokers

There does not seem to be an established biomarker for acetaldehyde exposure from smoking ([33], p. 1023). Acetaldehyde levels in blood are not different between smokers and nonsmokers [34-36]. Acetaldehyde is rapidly absorbed and completely metabolized in body tissue, mostly in mammalian liver tissue to acetic acid. Less than 5% of the absorbed compound is eliminated as the parent in expired air, and no excretion in the urine has been found [21]. Acetylaldehyde has a half-life of less than 15 minutes in the circulation [20, 21]. Almost quantitative retention (95-99%) of acetaldehyde occurs on inhalation of tobacco smoke during [37, 38].

If any acetaldehyde taken up by smoking would enter the circulation, it would have a half-life of only few minutes and an accumulation could be excluded [11].

List of abbreviations

3R4F	Kentucky 3R4F reference research cigarette [39]
ACToR	Aggregated Computational Toxicology Resource
AD	Addictive
ADME	Absorption and Distribution, Metabolism, and Excretion
Aldh	Aldehyde dehydrogenase
BoExp	Biomarkers of Exposure
CA	Carcinogen
CAS number	Chemical Abstracts Service number
CT	Cardiovascular toxicant
FDA	Food and Drug Administration
HC	Health Canada
HCI	Health Canada Intense regime [40]
HPHC	Harmful and Potentially Harmful Constituents
IARC	International Agency for Research on Cancer
ISO	International Organization for Standardization smoking regime [41]
IV	Intravenous
IUPAC	International Union of Pure and Applied Chemistry
MW	Molecular weight
NA	Not assessed
PMI	Philip Morris International
RDT	Reproductive or developmental toxicant

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RT	Respiratory toxicant
WHO	World Health Organization

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