APPENDIX A6.1.3.22 FORMALDEHYDE - FACTSHEET

	HPHC	BoExp assessed by PMI
IUPAC name	Methanal	N/A
Usual abbreviation	FA; FM	
Other names	Methyl aldehyde, methylene glycol, methylene oxide, formalin, formol, oxomethane, paraform, formic aldehlyde, oxymethylene, paraformaldehyde	
CAS number	50-00-0	
Formula and molecular weight	CH_2O MW: 30.03	

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

TABLE OF CONTENTS

APPENDIX A6.1.3.22 FORMALDEHYDE - FACTSHEET 1
Main characteristics 3
ADME properties 4
Exposure levels in smokers and non-smokers 6
List of abbreviations 7
References 8

TABLE OF FIGURES

Figure 1 Metabolic pathways of formaldehyde biotransformation 5

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

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 MSS (3R4F): 20µg/cigarette (ISO); 68.1µg/cigarette (HCI) [7] Smoke phase: mainly in gas/vapor phase [8-10] Presence in tobacco / pyrosynthesis (T°): present in uncombusted tobacco [11] / Pyrolysis of a US tobacco blend generated formaldehyde in one major temperature range, 200–400 °C, with small formation regions at about 400–550 °C and above 600 °C [12]. Precursors of formaldehyde in tobacco consist of various sugars [11, 13].
Other sources [14]	Formaldehyde is ubiquitous in the environment; it is an important endogenous chemical that occurs in most life forms, including humans. It is formed naturally in the troposphere during the oxidation of hydrocarbons. Formaldehyde's production and use in the manufacture of resins, disinfectants, preservatives, and a variety of other chemicals may result in its release to the environment through various waste streams. Formaldehyde's production and use as a fertilizer results in its direct release to the environment. The highest levels of airborne formaldehyde have been detected in indoor air, where it is released from various consumer products such as building materials and home furnishings [15].
Toxicity class (FDA) [1]	CA, RT
Toxicity – CA [6, 16]	IARC: group 1: carcinogenic to humans [17] Epidemiological studies of the relation of occupational exposure to formaldehyde and cancer at various sites provide sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans, strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde, and limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Toxicity – RT	Irritating effects in the upper respiratory tract; in sensitized subjects specific late asthmatic reactions may be provoked by brief exposures; nose/throat irritation, and eye irritation throughout the exposure; nasal flow resistance; laryngitis has also been reported as a reaction of exposure [18].
Toxicity – CT	-
Toxicity – RDT	Studies on reproductive hazards are mainly inconclusive [18].
Toxicity – AD	-
Toxicity - others	All available toxicity data can be found on the Website Aggregated Computational Toxicology Resource (ACToR) [19].

ADME properties

Absorption [20] – Formaldehyde vapors are readily absorbed from the respiratory tract. Due to rapid metabolism to formate, little, if any, intact formaldehyde can be found in the blood of humans or animals exposed to formaldehyde. Formaldehyde is also readily absorbed from the gastrointestinal tract and meets with the same metabolic fate as formaldehyde after inhalation exposure. The studies available in the open literature suggest that very little formaldehyde is absorbed via the dermal route. In all cases, absorption appears to be limited to cell layers immediately adjacent to the point of contact. Entry of formaldehyde into the blood (i.e., systemic absorption) occurs to a very limited extent, if at all.

Distribution [20] – No studies were located that describe the distribution of formaldehyde or its metabolites in humans after inhalation exposure, but the distribution of formaldehyde in laboratory animals has been reported. In rats, the terminal half-life of the ^{14}C has been shown to be around 55 hours, which was considerably longer than the known half-life of formaldehyde (about 1.5 minutes in humans [21]), indicating both the metabolism of $^{14}C\text{-}CH_2O$ to other molecules (i.e., formate) and incorporation into other molecules.

Metabolism [20] – Formaldehyde is an essential metabolic intermediate in all cells. It is produced during the normal metabolism of serine, glycine, methionine, and choline and also by the demethylation of N-, S-, and O-methyl compounds. Daily endogenous turnover of formaldehyde has been estimated to be around 878-1310 mg/kg bw per day [21]. Formaldehyde is rapidly metabolized and storage is not a factor in its toxicity (scheme is shown in Figure 1). The metabolism of formaldehyde to formate (via formaldehyde dehydrogenase, FDH) takes place in all of the tissues of the body as a consequence of endogenous formation of formaldehyde, and the formate is quickly removed by the supporting blood supply. FDH is the major metabolic enzyme involved in the metabolism of formaldehyde in all of the tissues studied; it is widely distributed in animal tissues, particularly in the rat nasal mucosa, and is specific for the glutathione adduct of formaldehyde. Formaldehyde dehydrogenase activity does not increase (i.e., not inducible) in response to formaldehyde exposure. Several other enzymes (i.e., nonspecific aldehyde dehydrogenase, S-formyl glutathione hydrolase (SFGS) and

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

catalase) can catalyze the reaction that oxidizes formaldehyde to formic acid. If formaldehyde is not metabolized enzymatically, then it can form cross linkages between proteins, between protein and single-stranded DNA or is incorporated into purines, thymidine, and amino acids via tetrahydrofolate-dependent one-carbon biosynthetic pathways.

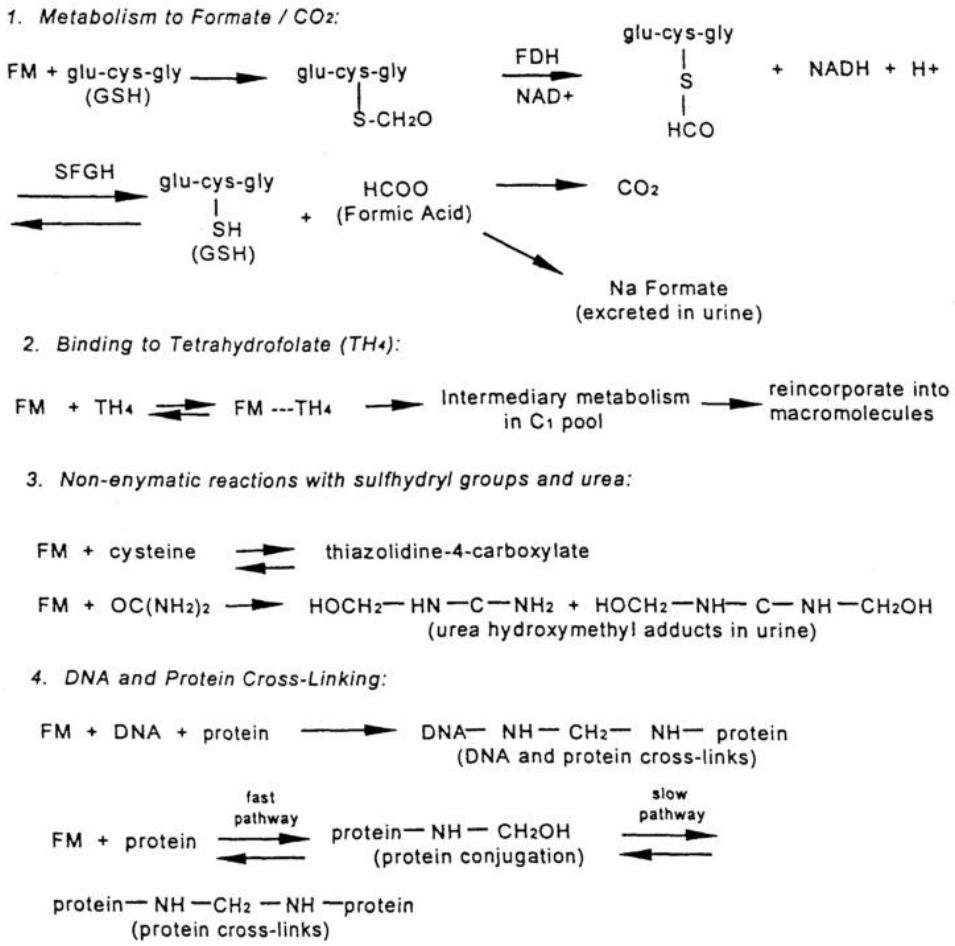


Figure 1 Metabolic pathways of formaldehyde biotransformation [20]

FM = formaldehyde; TH_4 = tetrahydrofolate; GSH = glutathione; NAD+ = nicotinamide adenosine dinucleotide; SFGS = S-formyl glutathione hydrolase; FDH = formaldehyde dehydrogenase.

Figure source: Agency for Toxic Substances and Disease Registry.

Excretion [20] – Being normal components of intermediary metabolism, neither formaldehyde nor formate are stored to any significant extent in any tissue of the body. Formate is either excreted in the urine (primarily as formic acid), incorporated into other cellular molecules, or oxidized to carbon dioxide and exhaled. Given the rapid conversion of formaldehyde to formate and subsequent incorporation into naturally occurring cellular constituents, excretion does not appear to be a factor in the toxicity of formaldehyde. The

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

toxicokinetics in all of the animals studied is similar across species lines. Formaldehyde half-life in humans is very short and has been estimated to be within 1-1.5 min [21].

Exposure levels in smokers and non-smokers

Exposure to formaldehyde comes from a number of atmospheric environments and makes it a poor marker of exposure to tobacco smoke, due to its lack of specificity. Potential for human exposure comes mainly from smoking (1 mg/day when smoking 20 cigarettes per day) [20]. Other sources are [20]: 1) environmental tobacco smoke (0.1-1 mg/day), 2) workplace (0.2-0.8 mg/day without occupational exposure and up to 5 mg/day with occupational exposure), 3) indoor air (0.5-2.0 or 1-10 mg/day for people staying 65% of their time in a conventional house or prefabricated house with chipboard, respectively) 4) outdoor air (0.02 mg/day for people staying 10% of their time outdoor). The short half-life of formaldehyde, its ubiquitous occurrence and endogenous formation prevent a reasonable approach for formaldehyde biomonitoring that would target smoke as a specific source, and thus explain the lack of publications with data on exposure levels in smokers vs. non-smokers. Most exposure assessments actually measure amount of formaldehyde in the environment, and not in the subjects exposed to this environment [22].

In a study where non-smoking human volunteers were exposed to 1.9 ppm of formaldehyde for 40 min, levels of formaldehyde in the blood were measure before and shortly after exposure [23]. Mean venous blood formaldehyde concentrations in humans prior to exposure showed a blood concentration of 2.61 ± 0.41 µg/g of blood. Individual variability was markedly present. Immediately after a 40-minute exposure, mean blood concentration of formaldehyde was 2.77 ± 0.28 µg/g of blood. There was thus no significant difference between pre- and post-exposure blood concentrations of formaldehyde at the formaldehyde air concentrations tested in this study. This result suggests that formaldehyde was absorbed only into the tissues of the respiratory tract. The absence of increased formaldehyde concentrations in the blood is likely due to its rapid metabolism in these tissues and/or fast reaction with cellular macromolecules.

Potential BoExp to formaldehyde, such as thiazolidine-carboxylic acid [24], DNA-protein cross links [25] or DNA adducts [26], are all affected by the large amounts of endogenous formaldehyde, as well as from the other sources of exposure to formaldehyde. This issue could be circumvented by conducting studies under very special conditions, such as using labelled precursors of formaldehyde.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

List of abbreviations

3R4F	Kentucky 3R4F reference research cigarette [27]
ACToR	Aggregated Computational Toxicology Resource
ADME	Absorption, distribution, metabolism, and excretion
AD	Addictive
BoExp	Biomarker of Exposure
CA	Carcinogen
CAS number	Chemical Abstracts Service number
CT	Cardiovascular toxicant
FDA	Food and Drug Administration
FDH	Formaldehyde dehydrogenase
FM	Formaldehyde
GSH	Glutathione;
HC	Health Canada
HCI	Health Canada Intense regime [28]
HPHC	Harmful and Potentially Harmful Constituents
IARC	International Agency for Research on Cancer
ISO	International Organization for Standardization smoking regime [29]
IUPAC	International Union of Pure and Applied Chemistry
MSS	Main stream smoke
MW	Molecular weight
N/A	Not applicable
NAD+	Nicotinamide adenosine dinucleotide
PMI	Philip Morris International
RDT	Reproductive or developmental toxicant
RT	Respiratory toxicant
SFGS	S-formyl glutathione hydrolase
TH_4	Tetrahydrofolate;
WHO	World Health Organization

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

References

[1] U.S. Department of Health and Human Services, FDA (Food and Drug Administration). [Docket No. FDA-2012-N-0143]: harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. Fed Regist. 2012; 77(64):20034-7.

[2] FDA (Food and Drug Administration). Guidance for industry - Reporting harmful and potentially harmful constituents in tobacco products and tobacco smoke under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act - Draft guidance. 2012.

[3] Health Canada. Tobacco reporting regulations. Modified 2011; Available from: http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/legislation/reg/indust/method/index-eng.php#main (Accessed on 21 May 2014).

[4] Health Canada. Consolidation - Tobacco reporting regulations. DORS/2000-273. 2013.

[5] WHO Study Group, Ashley DL, Ayo-Yusuf OA, Boobis AR, da Costa e Silva VL, Djordjevic MV, Gray N, Gupta P, Hammond SK, Hatsukami D, Henningfield J, Opperhuizen A, Zaatari G. WHO study group on tobacco product regulation - Report on the scientific basis of tobacco product regulations: fifth report of a WHO study group. 2015.

[6] WHO Study Group, Ashley DL, Burns D, Djordjevic M, Dybing E, Gray N, Hammond SK, Henningfield J, Jarvis M, Reddy KS, Robertson C, Zaatari G. The scientific basis of tobacco product regulation: second report of a WHO study group. World Health Organ Tech Rep Ser. 2008; (951):1-277, 1 p following

[7] Roemer E, Schramke H, Weiler H, Buettner A, Kausche S, Weber S, Berges A, Stueber M, Muench M, Trelles-Sticken E, Pype J, Kohlgrueber K, Voelkel H, Wittke S. Mainstream smoke chemistry and in vitro and in vivo toxicity of the reference cigarettes 3R4F and 2R4F. Beitrage zur Tabakforschung International/ Contributions to Tobacco Research. 2012; 25(1):316-35.

[8] Baker RR. Smoke generation inside a burning cigarette: modifying combustion to develop cigarettes that may be less hazardous to health. Progress in Energy and Combustion Science. 2006; 32(4):373-85.

[9] Spincer D, Chard BC. The determination of formaldehyde in cigarette smoke. Beiträge zur Tabakforschung / Contributions to Tobacco Research1971. p. 74.

[10] Pang X, Lewis AC. Carbonyl compounds in gas and particle phases of mainstream cigarette smoke. Sci Total Environ. 2011; 409(23):5000-9.

[11] Rodgman A, Perfetti TA. The chemical components of tobacco and tobacco smoke 2nd ed: CRC Press, Taylor & Francis Inc (United States); 2013.

[12] Baker RR, Coburn S, Liu C. The pyrolytic formation of formaldehyde from sugars and tobacco. Journal of Analytical and Applied Pyrolysis. 2006; 77(1):12-21.

[13] Baker RR. The generation of formaldehyde in cigarettes - Overview and recent experiments. Food Chem Toxicol. 2006; 44(11):1799-822.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

[14] National Center for Biotechnology Information (NCBI). Compound Summary for CID 712: formaldehyde. Available from: http://pubchem.ncbi.nlm.nih.gov/compound/712#section=Top (Accessed on 16 December 2014).

[15] U.S. environmental Protection Agency (EPA). Formaldehyde. 2000; Available from: http://www.epa.gov/ttn/atw/hlthef/formalde.html#ref1 (Accessed on 12 August 2014).

[16] U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Addendum to the toxicological profile for formaldehyde. 2010; Available from: http://www.atsdr.cdc.gov/toxprofiles/formaldehyde_addendum.pdf (Accessed on 13 AUgust 2014).

[17] IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. 2006; Vol. 88.

[18] Toxicology Data Network. Formaldehyde (CASRN: 50-00-0). 2006; Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~QQKZHh:3 (Accessed on 13 August 2014).

[19] Aggregated Computational Toxicology Resource (ACToR). Chemical summary: formaldehyde (50-00-0). Available from: http://actor.epa.gov/actor/GenericChemical?casrn=50-00-0 (Accessed on 15 September 2014).

[20] U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological profile for formaldehyde. 1999; Available from: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=220&tid=39 (Accessed on 13 August 2014).

[21] European Food Safety Authority (EFSA). Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources - Available from www.efsa.europa.eu/efsajournal (Accessed on 13 August 2014). EFSA Journal. 2014; 12 (2).

[22] Committee to Review the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens, Board on Environmental Studies and Toxicology, Division on Earth and Life Sciences, National Research Council. Review of the formaldehyde assessment in the National Toxicology Program 12th Report on carcinogens Washington (DC): National Academies Press (US); 2014.

[23] Heck HD, Casanova-Schmitz M, Dodd PB, Schachter EN, Witek TJ, Tosun T. Formaldehyde (CH2O) concentrations in the blood of humans and Fischer-344 rats exposed to CH2O under controlled conditions. Am Ind Hyg Assoc J. 1985; 46(1):1-3.

[24] Hemminki K. Urinary sulfur containing metabolites after administration of ethanol, acetaldehyde and formaldehyde to rats. Toxicol Lett. 1982; 11(1-2):1-6.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

[25] Shaham J, Bomstein Y, Meltzer A, Kaufman Z, Palma E, Ribak J. DNA-protein crosslinks, a biomarker of exposure to formaldehyde - In vitro and in vivo studies. Carcinogenesis. 1996; 17(1):121-5.

[26] Wang M, Cheng G, Balbo S, Carmella SG, Villalta PW, Hecht SS. Clear differences in levels of a formaldehyde-DNA adduct in leukocytes of smokers and nonsmokers. Cancer Res. 2009; 69(18):7170-4.

[27] Chepiga TA, Morton MJ, Murphy PA, Avalos JT, Bombick BR, Doolittle DJ, Borgerding MF, Swauger JE. A comparison of the mainstream smoke chemistry and mutagenicity of a representative sample of the US cigarette market with two Kentucky reference cigarettes (K1R4F and K1R5F). Food Chem Toxicol. 2000; 38(10):949-62.

[28] Health Canada, Tobacco Control Programme. Determination of "tar", nicotine and carbon monoxide in mainstream tobacco smoke. T-115. 1999; Available from: http://edge.rit.edu/edge/P10056/public/Health%20Canada%20Nicotine (Accessed on 06 January 2016).

[29] International Organization for Standardization (ISO). Routine analytical cigarette smoking machine - Definitions and standard conditions (ISO 3308:2012). Out of print. 2000; Revised version (2012) available from: http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=60404.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.