APPENDIX A6.1.3.9 1-AMINONAPHTHALENE - FACTSHEET

	HPHC	BoExp assessed by PMI (matrix)
IUPAC name	Naphthalen-1-amine	Parent compound, i.e. 1-NA (in urine)
Usual abbreviation	1-NA, 1-AN, 1AMNPT	
Other names	1-aminonaphthalene, 1-naphthylamine, alpha-naphthylamine, 1-naphthalamine, 1-naphthalenamine, naphthalidine, naphthalidam	
CAS number	134-32-7	
Formula and molecular weight	$C_{10}H_9N$ MW: 143.19	

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Main characteristics

Chemical class	Aromatic amine
HPHC lists	FDA-93 [1]; FDA-18 [2]; HC [3, 4]; PMI-58 ; WHO-39 [5]
Source in cigarettes	Amount in main stream smoke (3R4F): main source of exposure for general population [6, 7]; 13.6 ng/cigarette (ISO) [8]; 22.9 ng/cigarette (HCI) [8] Smoke phase: particulate phase [6] Presence in tobacco / pyrosynthesis (T°): not present in uncombusted tobacco / 25-900°C (naphthalene) [9]; main generation range 25-500°C [10]. Precursors are probably analogous to those of 2-aminonaphthalene, i.e. proteins, amino acids, pigments as well as nitrate [11].
Other sources [12, 13]	1-Aminonaphthalene (1-NA) has not been reported to occur naturally. 1-NA's production and use in toning prints made with cerium salts, agricultural chemicals, and as an intermediate in the synthesis of dyes, antioxidants, herbicides, some drugs, and other chemicals may result in its release to the environment through various waste streams. 1-Napthol is used for its production. 1-NA may also be emitted to the atmosphere in exhaust gases during its production and during the vulcanization of rubber mixtures. Monitoring data indicate that the general population may be exposed to 1-NA via contact with contaminated surface or groundwater or by inhalation of cigarette smoke.
Toxicity class (FDA) [1]	CA
Toxicity – CA [14]	IARC: group 3: unclassifiable as to carcinogenicity in humans [15]. 1-NA was plausibly concerned in several studies looking at workers exposed to 1-NA and the excess occurrence of cancers, but it was not possible to single out any compound from the combined exposure to arylamines. In view of the contamination of the commercial product and the mixed nature of the exposures investigated, it has not been possible to assess the carcinogenicity of 1-naphthylamine alone.
Toxicity – RT	-
Toxicity – CT	-

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Toxicity – RDT	-
Toxicity – AD	-
Toxicity - others	All available toxicity data can be found on the Website Aggregated Computational Toxicology Resource (ACToR) [16]. The substance is mildly irritating to the eyes and the skin.

ADME properties

Absorption and distribution [13] - 1-NA is absorbed through the skin and by inhalation. No data specific to distribution of 1-NA could be found.

Metabolism [13] - 1-NA is metabolized, by rats and other mammals, into 1-amino-2-naphthol and 1-amino-4-naphthol, which are excreted in urine as glucuronide and sulfate conjugates, together with the N-glucuronide, the N-sulfate, and the N-glucoside of 1-naphthylamine. A part of 1-NA is excreted unchanged: 0.2% from 5.0 mg dose was shown to be excreted in the urine (species not mentioned). In rhesus monkeys, the unoxidized 1-NA is excreted at a level 10 times that of 2-naphthylamine, indicating that it may be a poor substrate for the oxidative metabolic enzymes of the monkey: The N-hydroxy metabolite of 1-NA is suspected to be carcinogenic and mutagenic.

After oral administration of 71.6 mg/kg bw to female beagle dogs, a blood concentration of about 0.015 mg/mL after 60-80 min could be detected. Within 8 h, 25 mg unchanged 1-NA, and 0.5 mg of N-oxidation products were excreted in the urine. Another study in beagle dogs revealed the presence of small amounts of N-oxidation products in the urine, ranging from 2.85 to 125 µg following a dose of 1-naphthylamine of 15 mg/kg. This study was conducted over 9 years and showed no evidence of carcinogenicity at this dose of 15 mg/kg given (5 days a week) [17].

Excretion [13] - Half-life of 1-NA in humans has not been described in the literature. In rhesus monkeys, the N-hydroxy-N-glucuronide of 2-naphthylamine was excreted at a rate 6.8 times that of the 1-NA isomer (half-lives not mentioned). Furthermore, the unoxidized 1-naphthylamine is excreted at a level 10 times that of 2-NA, indicating that it may be a poor substrate for the oxidative metabolic enzymes of the monkey. The study by Radomski et al. in Beagle dogs has shown levels of 1-NA metabolites in urine that became close to zero in less than 8 hours [17]. Half-life was not calculated. Kinetics in humans is unlikely to differ much from other mammals, thus half-life of 1-NA in humans is probably also in the range of a few hours.

Exposure levels in smokers and non-smokers

Only very little data are available on levels of 1-NA in the urine of smokers and non-smokers (Table 1). In a study measuring 1-NA urinary levels in workers occupationally exposed to diesel engine exhaust, levels were higher in smokers (>100 ng/24 hours) than non-smokers (>10 ng/24 hours) (values not provided; only represented graphically) [18].

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Table 1 Representative urinary 1-NA levels in smokers and non-smokers

Author (year)	Levels in non-smokers (or ex-smokers)	Levels in smokers	Units; variability
Grimmer (2000) [19]	68.9 ± 105.4	506.7 ± 670.0	ng/24h; mean ± SD
Yu (2014) [20]	12.32 ± 8.91	67.02 ± 45.46	ng/24h; mean ± SD

List of abbreviations

3R4F	Kentucky 3R4F reference research cigarette [21]
1-NA	1-Aminonaphthalene, 1-naphthylamine
ACToR	Aggregated Computational Toxicology Resource
AD	Addictive
ADME	Absorption and Distribution, Metabolism, and Excretion
CA	Carcinogen
CAS number	Chemical Abstracts Service number
CT	Cardiovascular toxicant
FDA	Food and Drug Administration
HC	Health Canada
HCI	Health Canada Intense regime [22]
HPHC	Harmful and Potentially Harmful Constituents
IARC	International Agency for Research on Cancer
ISO	International Organization for Standardization smoking regime [23]
IUPAC	International Union of Pure and Applied Chemistry
MW	Molecular weight
PMI	Philip Morris International
RDT	Reproductive or developmental toxicant
RT	Respiratory toxicant
SD	Standard deviation
WHO	World Health Organization

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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] 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.

[7] Cole PV. Comparative effects of atmospheric pollution and cigarette smoking on carboxyhaemoglobin levels in man. Nature. 1975; 255(5511):699-701.

[8] Eldridge A, Betson TR, Gama MV, McAdam K. Variation in tobacco and mainstream smoke toxicant yields from selected commercial cigarette products. Regul Toxicol Pharmacol. 2015; 71(3):409-27.

[9] Baker RR. A review of pyrolysis studies to unravel reaction steps in burning tobacco. J Anal Appl Pyrolysis. 1987; 11(C):555-73.

[10] Torikai K, Yoshida S, Takahashi H. Effects of temperature, atmosphere and pH on the generation of smoke compounds during tobacco pyrolysis. Food Chem Toxicol. 2004; 42(9):1409-17.

[11] Piade JJ, Wajrock S, Jaccard G, Janeke G. 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. 2013; 55:329-47.

[12] Toxicology Data Network. 1-naphthylamine (CAS: 134-32-7). [Internet] Bethesda (MD): National Library of Medicine (US); Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+1080 (Accessed on 17 July 2014).

[13] National Center for Biotechnology Information (NCBI). Compound summary for CID 8640: 1-naphthylamine. 2014; Available from:

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http://pubchem.ncbi.nlm.nih.gov/compound/1-naphthylamine#section=Information-Sources (Accessed on 02 December 2014).

[14] U.S. Department of Health and Human Services. National Toxicology Program: CAS registry number: CAS No. 92-67-1 (4-aminobiphenyl). 2011; Available from: http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/aminobiphenyl.pdf (Accessed on 21 July 2014).

[15] IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: overall evaluations of carcinogenicity: an updating of IARC Monographs Volumes 1 to 42. 1998; Suppl. 7 Available from: http://monographs.iarc.fr/ENG/Monographs/suppl7/Suppl7-114.pdf (Accessed on 28 July 2015).

[16] Aggregated Computational Toxicology Resource (ACToR). Chemical summary: 1-naphthalenamine (134-32-7). Available from: http://actor.epa.gov/actor/GenericChemical?casrn=134-32-7 (Accessed on 15 September 2014).

[17] Radomski JL, Deichmann WB, Altman NH, Radomski T. Failure of pure 1-naphthylamine to induce bladder tumors in dogs. Cancer Res. 1980; 40(10):3537-9.

[18] Seidel A, Dahmann D, Krekeler H, Jacob J. Biomonitoring of polycyclic aromatic compounds in the urine of mining workers occupationally exposed to diesel exhaust. Int J Hyg Environ Health. 2002; 204(5-6):333-8.

[19] Grimmer G, Dettbarn G, Seidel A, Jacob J. Detection of carcinogenic aromatic amines in the urine of non-smokers. Sci Total Environ. 2000; 247(1):81-90.

[20] Yu J, Wang S, Zhao G, Wang B, Ding L, Zhang X, Xie J, Xie F. Determination of urinary aromatic amines in smokers and nonsmokers using a MIPs-SPE coupled with LC-MS/MS method. J Chromatogr B Analyt Technol Biomed Life Sci. 2014; 958:130-5.

[21] 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.

[22] 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).

[23] 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.

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