APPENDIX A6.1.3.10 2-AMINONAPHTHALENE - FACTSHEET

	HPHC	BoExp assessed by PMI (matrix)
IUPAC name	Naphthalen-2-amine	Parent compound, i.e. 2-NA (in urine)
Usual abbreviation	2-NA, 2-AN, 2AMNPT	
Other names	2-aminonaphthalene, 2-naphthylamine, beta-naphthylamine, 2-naphthalamine, 2-naphthalenamine	
CAS number	91-59-8	
Formula and molecular weight	C10H9N MW: 143.2	

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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]; WHO-18 [6]
Source in cigarettes	Amount in main stream smoke (3R4F): 5.69 ng/cigarette (ISO); 10.1 ng/cigarette (HCI) [7] Smoke phase: particulate phase [8, 9] Presence in tobacco / pyrosynthesis (T°): not present in uncombusted tobacco / 25-500°C [10]. Precursors in tobacco are proteins, amino acids, pigments as well as nitrate [11].
Other sources [12, 13]	2-aminonaphthalene (2-NA) is formed during the pyrolysis of nitrogen-containing organic matter and can occur as such in nature. It may occur in the waste streams from chemical industries where it is produced and used; it has been reported to be present in the effluent from certain dyestuff factories in Japan [14]. Occupational exposure to 2-NA mainly occurs during its production and when used in the manufacture of azo dyes. It can an also occur in laboratories where it is used for research purposes. 2-NAs former production and use in the manufacture of rubber and azo-dyes may have resulted in its direct release to the environment. Occupational exposure and general population exposure should be low or non-existent since 2-NA is no longer produced or used. The general population may still be exposed to 2-NA through the inhalation of cigarette smoke.
Toxicity class (FDA) [1]	CA
Toxicity – CA [15]	IARC: group 1: carcinogenic to humans [16] Due to the fact that most non-smoking-related 2-NA exposure occurred decades ago, there are only little exposure data beyond that from smoking to compare to [17]. It has been estimated that cigarette smoking accounts for 25-70% of all cases of bladder cancer in industrialized developed countries with aromatic amines such as 2-NA as the prime suspect causative carcinogen [18]. The incidence of second primary cancers was studied in 3322 employees who had worked from 1950-1978 in industries in Japan that manufactured 2-NA [19]. Of the 244 workers who had died of cancer of the genitourinary organs (first primary cancer),

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	11 (all male) had subsequent primary, histologically confirmed cancers of the liver, gallbladder, bile duct, large intestine and lung. No stomach cancer was observed in the study cohort. A statistically significant excess risk for liver, gall bladder, and bile duct cancer was found. The number of observed deaths from respiratory cancer was greater than expected, though not statistically significant. In an epidemiological study involving a cohort of 4,622 British dye workers, it was reported in 1954 that the increased bladder cancer deaths (26 cases; i.e 87 times higher than expected) in dye workers could by clearly attributed to 2-NA exposure [18]. The mean induction time was around 16 years. To date, at least seven epidemiological studies on dye workers with 2-NA exposure were reported from various countries throughout the world, with clear evidence of increased bladder cancer deaths in exposed workers; the observed cases/expected cases ratios ranged from 3.9 to 150, making it one of the most potent human bladder carcinogens [18, 20, 21]. In the last century, up to 100% of individuals involved in the purification of 2-NA for use in the dye industry developed bladder cancer [22].
Toxicity – RT	-
Toxicity – CT	-
Toxicity – RDT	-
Toxicity – AD	-
Toxicity - others	2-NA is mildly irritating to the skin and has produced contact dermatitis. All available toxicity data can be found on the Website Aggregated Computational Toxicology Resource (ACToR) [23].

ADME properties

Absorption and distribution - No information was found on the half-life of 2-NA in the body, on tissue distribution, and on its potential to accumulate upon repeated exposure.

Metabolism [22, 24] - The metabolism of 2-NA has been extensively studied. As many as 24 metabolites have been identified in the urine of various animal species. Like most carcinogenic aromatic amines, the first step of metabolic activation of 2-NA has been shown to be N-hydroxylation to yield reactive N-hydroxy-2-NA. Unlike 1-aminonaphthalene (1-NA), 2-NA can be N-hydroxylated in animals at substantially higher rates and at much lower doses. The second stage of metabolic activation involves

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further activation by N,O-transacetylation or O-acetylation to yield a highly reactive acyloxy derivative, which may generate a nitrenium ion. Alternatively, N-hydroxy-2-NA can be temporarily detoxified by glucuronidation to yield an unreactive glucuronide, which is then transported by the circulation to its site of action in the bladder (of humans and other susceptible animal species such as dogs and monkeys), where hydrolysis occurs enzymatically or by acid hydrolysis to regenerate the reactive intermediate. In addition, to the above metabolic activation pathway, there is also some evidence that the urinary bladder epithelium of humans and dogs may contain prostaglandin H synthase (PHS) [24], which can activate 2-NA to radicals, which may bind to DNA directly by undergoing nitrogen-nitrogen or nitrogen-carbon coupling reactions or indirectly by further one-electron oxidation to yield reactive diimines. The relative importance of the PHS pathway compared to the N-hydroxylation pathway is not clear.

The liver probably plays a major role in the metabolic activation of the bladder carcinogen 2-NA and in the inactivation of the non-carcinogenic isomer 1-NA. N-oxidation by cytochrome P450 enzymes is an initial step in the metabolic activation of aromatic amine compounds. Once metabolized, these compounds are converted to DNA-reactive species which can exhibit potent mutagenic and/or carcinogenic activity. The precise mechanism of P450 enzyme oxidation is not completely understood, although various theories, involving either one-electron transfer, two-electron transfer or addition-rearrangement, have been debated.

Excretion [22] - Because of the known carcinogenicity of 2-NA in humans, few metabolic studies have been carried out in humans. However, N-(2-naphthyl)-hydroxylamine and bis-(2-amino-1-naphthyl) phosphate have been identified in the urine of some hospital patients given small doses of 2-NA [16](p. 375). In addition, the excretion of the parent compound was determined in the urine of smokers and non-smokers [25-27].

A three-compartment pharmacokinetic model was developed to separate absorption, metabolism and distribution of N-hydroxy-2-NA in intact animal from events in bladder lumen (deposition, hydrolysis, and resorption). Total bladder exposure to carcinogen, N-hydroxy-2-aminonaphthalene, was simulated; and urine pH and voiding interval, both of which differ among species, were tested as variables. Relative species susceptibilities, indicated by model as total bladder exposure to hydroxy metabolites under conditions of normal urine pH and frequency of micturition for each species were: human ≥ dog > monkey > rat. This is consistent with reported carcinogenic potency of 2-NA in these species and suggests that urine pH and voiding interval are important factors in bladder cancer.

2-NA metabolism occurs through oxidation to form 2-amino-1-naphthol. At least 10 metabolites of 2-NA have been identified in the urine of rats and rabbits [22]. In both species, 70-80% of metabolites are removed with the urine, 20-30% are excreted in the feces. 2-NA is transformed into bis-(2-amino-1-naphthyl)hydrogen phosphate and excreted [22]. The hydrolysis of 2-NA to 2-amino-1-naphthol is thought to be responsible for the carcinogenic activity of 2-NA, as it was shown that species that are more susceptible to 2-NA carcinogenesis, such as dogs, are those that excrete more 2-amino-1-

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naphthol than the other species that are not as susceptible, such as mice, rats and rabbits [28].

Exposure levels in smokers and non-smokers

Differences in urinary 2-NA excretion between smokers and non-smokers were in the range of slightly more than one to about 10-fold (Table 1). The two oldest studies [25, 29] show by far the highest levels of 2-NA, probably because of methodological problems. In a study measuring 2-NA urinary levels in workers occupationally exposed to diesel engine exhaust, levels were similar between smokers and non-smokers (values not provided; only represented graphically) [30]. A recent study in which smokers consuming 20 cigarettes per day (cpd) or more were forced to smoke exactly 20, 15, 5 or 0 cpd during a 5-day confinement period showed a dose-relationship between the number of cigarettes and the levels of urinary 2-NA (i.e. 31.2, 21.6, 12.1 and 3.6 ng/24h, respectively) [31]. It was also shown that 2-NA urinary levels increased with tar yield, and also that they are strongly associated with cigarette consumption, increasing with higher consumption [26]. Lindner et al. have further shown a very good relationship between the urinary excretion of nicotine and its major metabolites (summarized as nicotine equivalents) and 2-NA [26].

2-NA has also been investigated in several studies in which switching from conventional cigarettes to either smoking cessation or to smoking an electrically heated cigarette smoking system occurred [32-35]. Within eight days, the urinary excretion of 2-NA dropped by 6- to 7-fold to a similar and relatively low level for both smoking cessation (Table 2) and switching [32, 36], reaching non-smokers' levels. A similar reduction in urinary 2-NA excretion was observed by switching from smoking to snus use [37]. All studies reported an appreciable background of 2-NA excretion in non-smokers and relatively broad variance within groups. The origin of 2-NA in the urine of current non-smokers is unknown. A possible source might be 2-nitronaphthaline, which may be generated by the combustion or pyrolysis of organic material, such as during cooking or in engine exhaust [38].

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Table 1 Representative urinary 2-NA levels in smokers and non-smokers

Author (year)	Levels in smokers	Levels in non-smokers (or ex-smokers)	Units; variability
Riffelmann (1995) [29]	3.1 ± 2.1	0.5 ± 0.7	µg/L; mean ± SD
Grimmer (2000) [25]	120.8 ± 279.2	84.5 ± 102.7	ng/24h; mean ± SD
Riedel (2006) [27]	20.8 ± 11.2	10.7 ± 9.5	ng/24h; mean ± SD
Lindner (2011) [26]	17.54 ± 50.88	1.79 ± 3.59	ng/24h; SD
Yu (2014) [39]	47.40 ± 50.68	10.18 ± 7.25	ng/24h; mean ± SD
Shepperd (2013) [40]	17.5 ± 7.6	1.6 ± 0.87	ng/24h; LS mean ± SD
Frost-Pineda (2008) [36]	17.9 ± 14.8	16.1 ± 8.5	ng/24h; mean ± SD

Table 2 Representative urinary 2-NA levels after smoking abstinence

Author (year)	Levels in smokers	Levels in ex-smokers or switchers	Units; variability
Frost-Pineda (2008) [36]	16.1 ± 8.5	2.2 ± 0.9 [a]	ng/24h; mean ± SD
Tricker (2012) [34]	7.5 ± 11.4	4.65 ± 1.57 [b]	ng/24h; mean ± SD
Tricker (2012) [32]	33.5 (11.0, 46.6)	5.5 (4.8, 7.0) [b]	ng/24h; median (Q25, Q75
Tricker (2012) [33]	40.8 ± 45.1	5.9 ± 3.9 [b]	ng/24h; mean ± SD
Theophilus (2015) [31]	36.4 ± 8.9	3.6 ± 1.4 [a]	ng/24h (mean ± SD)

[a] After 5 days of smoking abstinence

[b] After 8 days of smoking abstinence

List of abbreviations

3R4F	Kentucky 3R4F reference research cigarette [41]
2-NA	2-aminonaphthalene, 2-naphthylamine
ACToR	Aggregated Computational Toxicology Resource
AD	Addictive
ADME	Absorption and Distribution, Metabolism, and Excretion
CA	Carcinogen

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CAS number	Chemical Abstracts Service number
CT	Cardiovascular toxicant
FDA	Food and Drug Administration
HC	Health Canada
HCI	Health Canada Intense regime [42]
IARC	International Agency for Research on Cancer
ISO	International Organization for Standardization smoking regime [43]
IUPAC	International Union of Pure and Applied Chemistry
LS	Least squares
MW	Molecular weight
PMI	Philip Morris International
Q_{25}, Q_{75}	First and third quartile
RDT	Reproductive or developmental toxicant
RT	Respiratory toxicant
SD	Standard deviation
WHO	World Health Organization

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