APPENDIX A6.1.3.11 4-AMINOBIPHENYL - FACTSHEET

	HPHC	BoExp assessed by PMI (matrix)
IUPAC name	4-aminobiphenyl	Parent compound, i.e. 4-ABP (in urine)
Usual abbreviation	4-ABP	4-ABP
Other names	4-aminodiphenyl, (1,1'-biphenyl)-4-amine, p-biphenylamine, p-xenylamine, 4-biphenylamine, 4-phenylaniline	
CAS number	92-67-1	92-67-1
Formula and molecular weight	$C_{12}H_{11}N$ MW: 169.22	$C_{12}H_{11}N$ MW: 169.22

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 A6.1.3.11 4-AMINOBIPHENYL - FACTSHEET 1
Main characteristics 3
ADME properties 4
Exposure levels in smokers and non-smokers 6
List of abbreviations 8
References 9

TABLE OF TABLES

Table 1 Representative urinary 4-ABP levels in smokers and non-smokers 7
Table 2 Representative urinary 4-ABP levels after smoking abstinence or switching to a reduced toxicant prototype 8

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	Aromatic amine
HPHC lists	FDA-93 [1]; FDA-18 [2]; HC [3, 4]; PMI-58; WHO-39 [5]; WHO-18 [6]
Source in cigarettes	Main source of exposure to 4-aminobiphenyl for the general population Amount in mainstream smoke (3R4F): 1.01 ng/cigarette (ISO); 2.24 ng/cigarette (HCI) [7] Smoke phase: particulate phase [8] Presence in tobacco / Pyrosynthesis (T°): not present in uncombusted tobacco [9] / Main generation range 25-500°C [10], but higher temperature ranges ((~ 600-900 °C) were reported for measurable formation of 4-ABP [10-12].
Other sources [13, 14]	4-Aminobiphenyl can be found in hair dyes, food colorant, fungicide used on apples, fumes from cooking oils, and benzidine-contaminated sites. 4-Aminobiphenyl is not known to occur in nature. Occupational exposures are limited, as it has not been produced commercially in the USA since the mid-1950s. It was formerly used as a rubber antioxidant and dye intermediate.
Toxicity class (FDA) [1]	CA
Toxicity – CA [15]	IARC: group 1: carcinogenic to humans [13] Case reports and cohort-surveillances studies indicate a high occurrence of cancer of the urinary bladder in workers occupationally exposed to 4-ABP [13]. 4-Aminobiphenyl is carcinogenic in mice, rats, rabbits, and dogs. Bladder and liver tumors have been observed in mice, and bladder tumors have also been observed in rabbits and dogs following oral administration [16]. Mammary gland and intestinal tumors have been reported in rats exposed by subcutaneous injection [16]. Hemoglobin adducts of 4-ABP and 14 other aromatic amines have been determined in nonsmokers and smokers of blond- or black-tobacco cigarettes living in Turin, Italy. 4-ABP adduct levels were found to be significantly different in the three groups, with differences that were approximately proportional to the relative risk of bladder cancer of each group [17]. Adjustment for age and cigarette consumption did not materially influence the differences. A significant correlation of adduct levels with

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.

	cigarette consumption was also observed for all smokers as well as for smokers of blond tobacco [17, 18]. A study on workers in a chemical industry that manufactured 4-ABP showed that eleven percent of 171 workers developed bladder tumors. Tumors appeared 5-19 years after initial exposure, which ranged in duration from 1.25-10 years [19]. Cancer mortality was studied among 884 male workers at a chemical industry in West Virginia (USA) that produced a variety of chemicals [20]. A ten-fold increase in mortality from bladder cancer was reported, with all nine cases having started work before 4-aminobiphenyl production ceased in the plant in 1952.
Toxicity – RT	-
Toxicity – CT	-
Toxicity – RDT	-
Toxicity – AD	-
Toxicity - others	4-ABP is a skin and eye irritant. Exposure to 4-ABP can cause headache, lethargy, urinary tract symptoms [21]. All available toxicity data can be found on the Website Aggregated Computational Toxicology Resource (ACToR [22])

ADME properties

Absorption and Distribution [23]– 4-ABP can be absorbed into the body by inhalation, through the skin and by ingestion. DNA adducts with 4-ABP can been found in urinary bladder, exfoliated bladder cells, placenta, laryngeal tissue and hepatocellular carcinoma biopsies from cigarette smokers [24-26].

Metabolism [13] - Multiple metabolic pathways are involved in the activation of aromatic amines to DNA-reactive intermediates [27]. Metabolism is initiated in the liver with either N-oxidation (by cytochrome P-450-associated enzymes) or N-acetylation (by N-acetyltransferase 2, NAT2). N-oxidation to N-hydroxyarylamine is mainly mediated by CYP1A2, but also CYP1A1 and CYP4B1 iso-enzymes may play a role. NAT2-catalysed N-acetylation can provide a detoxification pathway for aromatic amines since it reduces the amount of parent compound that may undergo CYP-mediated N-hydroxylation. The N-hydroxy metabolite is highly electrophilic: N-hydroxyaminobiphenyl, the oxidation product of 4-aminobiphenyl (4-ABP) forms adducts with hepatic DNA in rats. N-hydroxyarylamines may be transported in free form to the blood or be conjugated with glucuronide. N-acetyltransferase 1 (NAT1)-mediated O-acetylation may represent the final activation step of N-hydroxyarylamines, taking place in the bladder epithelium and forming N-acetoxyarylamine.

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.

A significant amount of the N-hydroxyarylamine can enter the blood stream where it is further oxidized to form the nitroso compound. During this reaction, methemoglobin is formed, particularly with single ring aromatic amines. The nitroso compound may react with cysteine residues in hemoglobin to form hemoglobin adducts [27].

Other activation pathways of aromatic amines to DNA-reactive intermediates include the sulfotransferase-mediated activation of N-hydroxyarylamine to an N-sulfate ester, the myeloperoxidase and lactoperoxidase-mediated pathways that catalyse activation in the mammary gland, the peroxidative activation by prostaglandin H synthase, likely predominant in extra-hepatic tissues with low levels of cytochrome P450 isoenzymes, and non-enzymatic protonation of the N-hydroxylamine nitrogen. Genotoxic aromatic amines may induce tumour formation at different sites depending on substrate specificity and different bio-activation pathways. Inter-individual variability in prostaglandin H synthases in the urinary bladder and in myeloperoxidases in the lung may account for differences in target-site susceptibility to aromatic amines in cigarette smokers.

The genotoxic effects of aromatic amines including 4-ABP are well established on the basis of mutagenicity and clastogenicity observed in *in vitro* and *in vivo* assays that show the capability of these compounds to form DNA adducts after metabolic activation to electrophilic intermediates [28]. As DNA adducts may lead to somatic point mutations if not repaired, it is reasonable to assume that activated aromatic amines may lead to bladder tumour development by inducing mutations in key genes such as the TP53 tumour suppressor gene and the H-RAS gene, which are both involved in bladder carcinogenesis [28]. Organ specificity and inter- and intra-species differences in cancer susceptibility to aromatic amines are likely related to polymorphisms in genes that regulate DNA-repair, since deficient DNA-repair capacity is associated with increased bladder cancer risk, and to polymorphisms in genes that encode enzymes involved in activation or detoxification pathways. The NAT2 slow-acetylator genotype accounts for a greater risk for cancer of the urinary bladder in individuals exposed to 4-ABP [28]. Conflicting findings between studies may be a consequence of the interdependence of pathways of arylamine metabolism and of the capability of N-acetyltransferases both to detoxify the parent compound and to activate metabolites at different rates in different tissues.

Excretion [13] - Seyler et al. [29] report that no 4-ABP metabolites have been positively identified in human urine, thus biomarkers to estimate the internal dose of 4-ABP rely solely on the presence of the parent compound in urine. Talaska and Al-Zoughool [30] have suggested a metabolic pathway for 4-ABP in which the toxicant is converted to N-acetyl or glucuronide forms in the liver and subsequently eliminated via renal excretion. The acid-labile glucuronidated intermediate is then excreted via the kidney and hydrolysed in the bladder lumen where it eventually forms the N-hydroxy metabolite again. The acidic pH of urine enhances the hydrolysis reaction and thus represents an additional risk factor for aromatic amine-related bladder cancer [31]. NAT1-mediated O-acetylation may represent the final activation step of N-hydroxyarylamines; it takes place in the bladder epithelium and forms N-acetoxyarylamine. Breakdown of this unstable aromatic acetoxy ester produces the highly reactive aryl nitrenium ion that may serve as electrophilic intermediate leading to DNA adducts and tumour initiation.

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}C]4-ABP administered orally to rats at 100 mg/kg gave elimination half-lives of 31, 36.7 and 34h, for urinary, fecal and total ^{14}C elimination, respectively [32]. 77% of ^{14}C activity was excreted in 48h with a half-life of 15h and 23% with a half-life of 180 h. In another study, 5.61 mg of [^{3}H]4-ABP was injected intraperitoneally, Semi-log plots of percentage dose remaining in the body versus time indicated that 82% of ^{3}H activity was excreted in 36h with a half-life of 14.4h and 18% with a half-life of 46.2h [32].

Wide variations in human CYP1A2 activity have been reported in different populations, however, the variant alleles identified so far in the structural gene do not explain the activity range reported. Differences in activity can go from 40- to 130-fold [33]. In Japanese, differences of 14-fold in the CYP1A2 activity were reported [34]. Constitutional factors and enzyme induction/inhibition may explain these differences, but also basal levels of expression. mRNA levels of 12 different human liver samples showed differences of up to 12-fold. In vitro hepatic microsomal activity using different human samples showed differences in N-oxidation of 4-aminobiphenyl of up to 44-fold [35]. These differences in CYP1A2 activity are likely to affect the urinary levels of 4-ABP in different populations.

Exposure levels in smokers and non-smokers

Grimmer et al. [36] and Riedel et al. [27] found no or small difference in urinary 4-ABP concentrations between smokers and nonsmokers (1.1 and 1.6 fold difference, respectively) (Table 1). On the other hand, other studies reported urinary 4-ABP levels in smokers from three to nine times higher than in nonsmokers [29, 37-41] (Table 1). A moderate correlation between the urinary excretion of 4-ABP in smokers and the extent of smoking, measured by daily cigarette consumption was found [37]. 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 4-ABP (i.e. 22.4, 16.6, 10.9 and 5.5 ng/24h, respectively) [39]. In a study by Grimmer et al., smokers were reported to excrete amounts of 4-ABP in the urine similar to those of non-smokers [36]. In this study, exposure to environmental tobacco smoke or diesel exhaust could be excluded as a source of 4-ABP in the non-smokers, since only low levels of cotinine and no diesel exhaust-related nitroarenes nor the corresponding amino-derivatives, respectively, were found in the urine of the non-smokers. In a later study, 4-ABP could not be detected in the 12-h urine samples of persons without known exposure to aromatic amines [42]. In a more recent study statistically significantly different urinary 4-ABP levels of 9.6 ± 4.9 ng/24h in non-smokers and of 15.3 ± 7.3 ng/24h in smokers were reported [27]. In the same study a moderate correlation between the urinary excretion of 4-ABP in smokers and the extent of smoking, measured by daily cigarette consumption, was found. In another study, the geometric mean of the 4-ABP concentration in urine, collected once during the day, was reported at 1.64 pg/mg creatinine and 8.69 pg/mg creatinine for non-smokers and smokers, respectively [29]. The authors suggested that following tobacco smoke exposure, total urinary 4-ABP is a reliable biomarker of exposure to this carcinogen [29]. Some of the inconsistent findings in the urinary 4-ABP levels between smokers and non-smokers [29] might be partially explained by the different sensitivities of the methods used for the analyses.

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.

In six studies with smoking abstinent groups, the change of urinary excretion of 4-ABP was about 2- to 5-fold after 5 or 8 days of smoking abstinence, which is consistent with the order of magnitude observed between smokers and non-smokers [43-48] (Table 2). Sarkar et al. [49] reported higher differences in urinary 4-ABP levels after 8 days in confinement, both for active smokers who abstained from smoking or for those who switched to a smokeless product, i.e. about 8-fold. A comparable order of reduction was found by Frost-Pineda et al., after 8 days of smoking abstinence [47]. Shepperd et al. found a similar decrease, i.e. of 4-ABP of about 7-fold, after 14 days in subjects who switched from CC to reduced toxicant prototype cigarettes [50], while a reduction of 5-fold was observed with another prototype, over the same period of time [47].

Higher levels of hemoglobin adducts are found in smokers than non-smokers, but because of the long half-lives of these adducts, they are usually not considered in short-term studies [26].

Table 1 Representative urinary 4-ABP levels in smokers and non-smokers

Author (year)	Levels in smokers	Levels in non-smokers (or ex-smokers)	Units; variability
Lindner (2011) [37]	24.66 ± 74.44	2.77 ± 11.79	ng/24h; mean ± SD
Scherer (2014) [38]	19.5 ± 8.5	2.2 ± 2.6 (2.1 ± 1.7)[a]	ng/24h; mean ± SD
Grimmer (2000) [36]	78.6 ± 85.2	68.1 ± 91.5	ng/24h; mean ± SD
Riedel (2006) [27]	15.3 ± 7.3	9.6 ± 4.9	ng/24h; mean ± SD
Seyler (2011) [29]	8.69 (7.43–10.16)	1.64 (1.30–2.07)	pg/mg creat; geometric mean (95% CI)
Yu (2014) [40]	17.27 ± 13.16	5.58 ± 2.90	ng/24h; mean ± SD
Miura (2015) [41]	11.0 ± 7.37	1.43 ± 1.39	ng/24h; mean ± SD

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 2 Representative urinary 4-ABP levels after smoking abstinence or switching to a reduced toxicant prototype

Author (year)	Levels in smokers	Levels in ex-smokers or switchers	Units; variability
Shepperd (2013) [50]	13.9 ± 7.1 (3.1-33.0)	2.0 ± 1.0 (0.5–4.9) [a]	ng/24h; LS means ± SD (ranges)
Tricker (2012) [43]	10.4 ± 5.7	4.7 ± 1.6 [b]	ng/24h; mean ± SD
Tricker (2012) [44]	11.4 (7.1, 14.6)	5.5 (4.8, 7.0) [c]	ng/24h; median (Q_{25}, Q_{75})
Tricker (2012) [45]	15.2 ± 8.6	4.6 ± 1.9 [c]	ng/24h; mean ± SD
Sarkar (2010) [49]	19.61 ± 10.67	2.25 ± 0.88 [c]	ng/24h; mean ± SD
Sarkar (2010) [49]	23.04 ± 10.43	2.91 ± 0.92 [d]	ng/24h; mean ± SD
Theophilus (2015) [46]	27.8 ± 7.9	5.5 ± 2.7 [b]	ng/24h; mean ± SD
Sakaguchi (2014) [48]	14.5 ± 5.43	3.95 ± 1.74 [e]	ng/24h; mean ± SD
Frost-Pineda (2008) [47]	10.8 ± 16.5	2 ± 1.1 [c]	ng/24h; mean ± SD

[a] After 14 days of switching to reduced toxicant prototype cigarette
[b] After 5 days of smoking abstinence
[c] After 8 days of smoking abstinence
[d] After 8 days Marlboro snus use
[e] After 14 days of switching to reduced toxicant prototype cigarette

List of abbreviations

2-NA	2-aminonaphthalene, 2-naphthylamine
3R4F	Kentucky 3R4F reference research cigarette [51]
ACToR	Aggregated Computational Toxicology Resource
AD	Addictive
ADME	Absorption and Distribution, Metabolism, and Excretion
CA	Carcinogen
CAS number	Chemical Abstracts Service number
CC	Conventional Cigarette / Combustible Cigarette
Ci	Confidence interval
CT	Cardiovascular toxicant
Creat	Creatinine

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.

CYP1A1	Cytochrome P450 1A1
CYP1A2	Cytochrome P450 1A2
CYP4B1	Cytochrome P450 4B1
FDA	Food and Drug Administration
H-RAS	Harvey rat sarcoma viral oncogene homolog
HC	Health Canada
HCI	Health Canada Intense regime [52]
HPHC	Harmful and Potentially Harmful Constituents
IARC	International Agency for Research on Cancer
ISO	International Organization for Standardization smoking regime [53]
IUPAC	International Union of Pure and Applied Chemistry
LS	Least squares
MW	Molecular weight
NAT1	N-acetyltransferase 1
NAT2	N-acetyltransferase 2
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

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.

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.

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

[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] Stabbert R, Schafer KH, Biefel C, Rustemeier K. Analysis of aromatic amines in cigarette smoke. Rapid Commun Mass Spectrom. 2003; 17(18):2125-32.

[13] IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: chemical agents and related occupations. 2012; Vol. 100F.

[14] National Center for Biotechnology Information (NCBI). Compound summary for CID 7102: 4-biphenylamine. 2014; Available from: http://pubchem.ncbi.nlm.nih.gov/compound/7102#section=Top (Accessed on 11 December 2014).

[15] U.S. Department of Health and Human Services. National Toxicology Program: CAS registry number: CAS No. 92-67-1 (4-aminobiphenyl). 2011; Available

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.

from: http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/aminobiphenyl.pdf (Accessed on 21 July 2014).

[16] U.S. environmental Protection Agency (EPA). 4-Aminobiphenyl 92-67-1: hazard summary. 2000; Available from: http://www.epa.gov/ttnatw01/hlthef/aminobip.html (Accessed on 11 December 2014).

[17] Bryant MS, Vineis P, Skipper PL, Tannenbaum SR. Hemoglobin adducts of aromatic amines: associations with smoking status and type of tobacco. Proc Natl Acad Sci U S A. 1988; 85(24):9788-91.

[18] Bryant MS, Skipper PL, Tannenbaum SR, Maclure M. Hemoglobin adducts of 4-aminobiphenyl in smokers and nonsmokers. Cancer Res. 1987; 47(2):602-8.

[19] Toxicology Data Network. 4-Biphenylamine (CASRN: 92-67-1). [Internet] Bethesda (MD): National Library of Medicine (US); Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~idaM5d:3 (Accessed on 21 July 2014).

[20] IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: some aromatic amines, organic dyes, and related exposures. 4-Aminobiphenyl. 2010; Vol 99:71-108.

[21] CDC (Centers for Disease Control). Occupational safety and health guideline for 4-aminodiphenyl potential human carcinogen. 1988.

[22] Aggregated Computational Toxicology Resource (ACToR). Chemical summary: 4-aminobiphenyl (92-67-1). ; Available from: http://actor.epa.gov/actor/GenericChemical?casrn=92-67-1 (Accessed on 15 September 2014).

[23] International Programme on Chemical Safety (IPCS). 4-Aminobiphenyl (ICSC: 0759). 2007; Available from: http://www.inchem.org/documents/icsc/icsc/eics0759.htm (Accessed on 17 July 2014).

[24] National Center for Biotechnology Information (NCBI). Compound Summary for CID 7102: 4-aminobiphenyl. 2015; Available from: http://pubchem.ncbi.nlm.nih.gov/compound/7102#section=Top (Accessed on 06 January 2015).

[25] Talaska G, Schamer M, Skipper P, Tannenbaum S, Caporaso N, Unruh L, Kadlubar FF, Bartsch H, Malaveille C, Vineis P. Detection of carcinogen-DNA adducts in exfoliated urothelial cells of cigarette smokers: association with smoking, hemoglobin adducts, and urinary mutagenicity. Cancer Epidemiol Biomarkers Prev. 1991; 1(1):61-6.

[26] Talaska G, al-Juburi AZ, Kadlubar FF. Smoking related carcinogen-DNA adducts in biopsy samples of human urinary bladder: identification of N-(deoxyguanosin-8-yl)-4-aminobiphenyl as a major adduct. Proc Natl Acad Sci U S A. 1991; 88(12):5350-4.

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.

[27] Riedel K, Scherer G, Engl J, Hagedorn HW, Tricker AR. Determination of three carcinogenic aromatic amines in urine of smokers and nonsmokers. J Anal Toxicol. 2006; 30(3):187-95.

[28] IARC (International Agency for Research on Cancer). Monographs on the evaluation of carcinogenic risks to humans: chemical agents and related occupations. 4-Aminobiphenyl. 2010; Vol 99:71-108. 2012; 100F.

[29] Seyler TH, Bernert JT. Analysis of 4-aminobiphenyl in smoker's and nonsmoker's urine by tandem mass spectrometry. Biomarkers. 2011; 16(3):212-21.

[30] Talaska G, Al-Zoughool M. Aromatic amines and biomarkers of human exposure. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2003; 21(2):133-64.

[31] Sarkar MA, Nseyo UO, Zhong BZ. Mutagenic outcome of the urinary carcinogen 4-aminobiphenyl is increased in acidic pH. Environ Toxicol Pharmacol. 2002; 11(1):23-6.

[32] Karreth S, Lenk W. The metabolism of 4-aminobiphenyl in rat. I. Reaction of N-hydroxy-4-aminobiphenyl with rat blood in vivo. Xenobiotica. 1991; 21(3):417-28.

[33] McGraw J, Waller D. Cytochrome P450 variations in different ethnic populations. Expert Opin Drug Metab Toxicol. 2012; 8(3):371-82.

[34] Nakajima M, Yokoi T, Mizutani M, Shin S, Kadlubar FF, Kamataki T. Phenotyping of CYP1A2 in Japanese population by analysis of caffeine urinary metabolites: absence of mutation prescribing the phenotype in the CYP1A2 gene. Cancer Epidemiol Biomarkers Prev. 1994; 3(5):413-21.

[35] Butler MA, Guengerich FP, Kadlubar FF. Metabolic oxidation of the carcinogens 4-aminobiphenyl and 4,4'-methylene-bis(2-chloroaniline) by human hepatic microsomes and by purified rat hepatic cytochrome P-450 monooxygenases. Cancer Res. 1989; 49(1):25-31.

[36] 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.

[37] Lindner D, Smith S, Leroy CM, Tricker AR. Comparison of exposure to selected cigarette smoke constituents in adult smokers and nonsmokers in a European, multicenter, observational study. Cancer Epidemiol Biomarkers Prev. 2011; 20(7):1524-36.

[38] Scherer G, Newland K, Papadopoulou E, Minet E. A correlation study applied to biomarkers of internal and effective dose for acrylonitrile and 4-aminobiphenyl in smokers. Biomarkers. 2014; 19(4):291-301.

[39] Roethig HJ, Munjal S, Feng S, Liang Q, Sarkar M, Walk RA, Mendes PE. Population estimates for biomarkers of exposure to cigarette smoke in adult U.S. cigarette smokers. Nicotine Tob Res. 2009; 11(10):1216-25.

[40] 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.

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.

[41] Miura N, Yuki D, Minami N, Kakehi A, Futamura Y. A study to investigate changes in the levels of biomarkers of exposure to selected cigarette smoke constituents in Japanese adult male smokers who switched to a non-combustion inhaler type of tobacco product. Regul Toxicol Pharmacol. 2015.

[42] Weiss T, Angerer J. Simultaneous determination of various aromatic amines and metabolites of aromatic nitro compounds in urine for low level exposure using gas chromatography-mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2002; 778(1-2):179-92.

[43] Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-day randomized clinical trial of a menthol cigarette in Japan. Regul Toxicol Pharmacol. 2012; 64:S64-S73.

[44] Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: eight-day randomized clinical trial in Korea. Regul Toxicol Pharmacol. 2012; 64(2 Suppl):S45-53.

[45] Tricker AR, Kanada S, Takada K, Leroy CM, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 5: 8-Day randomized clinical trial in Japan. Regul Toxicol Pharmacol. 2012; 64(2):S54-S63.

[46] Theophilus EH, Coggins CRE, Chen P, Schmidt ER, Borgerding MF. Magnitudes of biomarker reductions in response to controlled reductions in cigarettes smoked per day: a one-week clinical confinement study. Regul Toxicol Pharmacol. 2015; 71(2):225-34.

[47] Frost-Pineda K, Zedler BK, Oliveri D, Feng S, Liang Q, Roethig HJ. Short-term clinical exposure evaluation of a third-generation Electrically Heated Cigarette Smoking System (EHCSS) in adult smokers. Regul Toxicol Pharmacol. 2008; 52:104-10.

[48] Sakaguchi C, Kakehi A, Minami N, Kikuchi A, Futamura Y. Exposure evaluation of adult male Japanese smokers switched to a heated cigarette in a controlled clinical setting. Regul Toxicol Pharmacol. 2014.

[49] Sarkar M, Liu J, Koval T, Wang J, Feng S, Serafin R, Jin Y, Xie Y, Newland K, Roethig HJ. Evaluation of biomarkers of exposure in adult cigarette smokers using Marlboro snus. Nicotine Tob Res. 2010; 12(2):105-16.

[50] Shepperd CJ, Eldridge A, Camacho OM, McAdam K, Proctor CJ, Meyer I. Changes in levels of biomarkers of exposure observed in a controlled study of smokers switched from conventional to reduced toxicant prototype cigarettes. Regul Toxicol Pharmacol. 2013; 66(1):147-62. Erratum in Regul Toxicol Pharmacol. 2013;67(3):536.

[51] 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.

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.

[52] 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).

[53] 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.