Estimated HPHC Intakes from Snus Consumption – Comparison with Dietary Intakes or Smoking

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1 Introduction

More than 8,000 different components have been identified in tobacco and tobacco smoke (Rodgman and Perfetti 2009). Because of the extensive number present in tobacco products and the complexity of the mixture, research efforts over the last decades have been made to establish the components that cause or contribute to tobacco-use associated disease and to identify those that contribute most. It is thought that "for many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible" (IOM 2012). In this context, several regulatory agencies and researchers have established or proposed priority lists of components for analysis and regulation based on their prevalence and potency to cause disease (e.g., Ayo-Yusuf and Connolly 2011; Burns et al. 2008; Cunningham et al. 2011; Fowles and Dybing 2003).

In April 2012, the U.S. FDA released a list of "Harmful or Potentially Harmful Constituents (HPHC)" that it determined can cause direct or indirect harm. This list is based on lists previously established by other public health agencies (e.g., WHO 2009) and currently consists of 93[1] components, listed as associated with at least one of five different disease outcomes (cancer, cardiovascular disease, respiratory effects, developmental or reproductive effects, and addiction) (FDA 2012).

Many of the chemicals on the current list are routinely analyzed in tobacco smoke. However, since STPs are not combusted, components yielding from this process are not present in STPs. Accordingly, a substantially lower number of components have been quantified in STPs compared to tobacco smoke. Of the 93 components on the current HPHC list, 43 are thought to originate from combustion of tobacco or have never been quantified comprehensively in STPs. These include aromatic amines[2], volatile hydrocarbons[3], some carbonyls[4], and inorganics[5], phenols[6], heterocyclic aromatic amines[7], chlorinated dioxins and furans, other aromatic components[8], small organic components[9], and some epoxides[10]. These components are not further discussed in the present report.

The remaining 50 components together with additional components that have been quantified or were considered relevant to STPs are considered in the following sections. A brief description of potential health effects associated with the components and analytical data available from the scientific literature for traditional Swedish snus and other STPs is presented in the *ENVIRON*

[1] The count of 93 components is based on the following: stereoisomers of cresol (*o*-, *m*-, *p*-), metals/metalloids and their compounds, as well as chlorinated dioxins and furans were not counted separately.
[2] 4-Aminobiphenyl, 1-aminonaphthalene, 2-aminonaphthalene, *o*-anisidine, *o*-toluidine, 2,6-dimethylaniline
[3] Acrylonitrile, 1,3-butadiene, benzene, ethylbenzene, isoprene, styrene, toluene
[4] Acetone, methyl ethyl ketone, propionaldehyde
[5] Carbon monoxide, hydrogen cyanide, hydrazine
[6] Catechol, cresols (o, m, p), phenol
[7] A-α-C (2-Amino-9H-pyrido[2,3-b]indole), Glu-P-1 (2-Amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole), Glu-P-2 (2-Aminodipyrido[1,2-a:3',2'-d]imidazole), IQ (2-Amino-3-methylimidazo[4,5-f]quinoline), MeA-α-C (2-Amino-3-methyl)-9H-pyrido[2,3-b]indole), PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine), Trp-P-1 (3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole), Trp-P-2 (1-Methyl-3-amino-5H-pyrido[4,3-b]indole)
[8] Caffeic acid, coumarin (banned in food), furan, nitrobenzene, quinoline
[9] Acetamide, nitromethane, 2-nitropropane, vinyl acetate, vinyl chloride
[10] Ethylene oxide, propylene oxide

Update Review of the Scientific Literature on Snus (ENVIRON Snus Monograph 2013), Section 2 and Appendix II.

2 Objective

The purpose of this analysis is to compare the estimated daily intakes of HPHCs from snus consumption to their intakes from the diet. No comparisons with diet were made for exposure to tobacco-specific nitrosamines (TSNAs) and nicotine, because of their negligible amounts in foods relative to tobacco. For TSNAs, the estimated intake from snus is compared with the estimated exposure from smoking. The available published risk assessments for HPHCs in snus are also examined. For the alkaloids, including nicotine, only intake estimates for snus consumption are presented. For a comparison of nicotine intake from snus consumption and smoking, the reader is referred to nicotine pharmacokinetic and biomarker data in the ENVIRON Snus Monograph (2013), Appendix 3, Section A III 3.1.

These comparisons will support the data from epidemiological studies to inform the FDA Modified Risk Tobacco Product Application (MRTPA) Key Area of Investigation "Health Risk of the Tobacco Product". In particular, for TSNAs, the comparisons will inform "the health risk associated with use of the proposed MRTP as compared to using other tobacco products on the market […]", i.e., smoking [part A]; for the other HPHCs, the comparisons will inform "the health risks associated with initiating use of the proposed MRTP as compared to never using tobacco products" [part F]. Though health risks are not quantified, the information on relative oral exposures from Swedish Match's snus products compared to that from foods for the general adult population provides context on the potential contribution to total exposures from use of these tobacco products.

3 Methods

3.1 Approach to Estimate HPHC Intakes from Snus Consumption

The average concentrations detected in each of the eight snus products were obtained from the Swedish Match report, "Swedish snus according to GOTHIATEK®" (SM GOTHIATEK report 2013, page 121, Table 7:21, *Chemical data on the snus products on the US market derived from the Brands Testing Program in 2012.*). Because no maximum concentrations were available specific to the eight products at the time of the present analysis, the maximum concentrations provided for many of the HPHCs in Table 7:20*, The arithmetic means, minimum and maximum values for the analytes tested on 45 snus products included in the Brands Testing Program in 2011* (SM GOTHIATEK report 2013, page 119) were used to calculate a worst case exposure scenario. This calculation is applied to estimate an "upper bound" intake for each of the eight products after adjusting to the moisture of each product. This represents a "worst case" estimate, that is, it answers the question, what if a heavy (upper bound) user of snus consistently used a Swedish Match product that contained the highest concentration of this component?

Intake estimates from snus consumption were calculated based on the following assumptions:

- Concentrations reported as below the limit of detection (LOD) were estimated as LOD/√2) (Hornung and Reed 1990); accordingly concentrations below the limit of

quantitation (LOQ) are taken into account as LOQ/√2 (EPA 2000). It is recognized that summing multiple concentrations below the LOD in this manner is likely to lead to a very conservative estimate.

- Mean and 95th percentile daily snus consumption data (g/day, calculated from packages or portions, whichever is higher) was obtained from Digard et al. (2009) (pouched snus users (all): 12 and 24 g/day, respectively; loose snus users (all): 32 and 77 g/day, respectively). In addition, because of its substantially lower pouch weight of 0.33 g, consumption for *General Dry Mint PSOM* was also estimated assuming an average of 12 portions/day. For three products that had slightly lower pouch weight than 1 g (as per data provided by Swedish Match), estimates were based on a g/day intake basis regardless (*General Mint PSWL*, *General Nordic Mint PSWL*, *General Classic Bland PSWL* with 0.943, 0.918, 0.881 g/pouch, respectively). A mean portion weight of 2.65 g is assumed for loose snus.

- Where available, data for the extraction of components (in %) from snus was used (as reviewed in the ENVIRON Snus Monograph 2013 (Section 2). Where specific data were not available, conservatively, 100% extraction was assumed. The available studies show that extraction varies substantially between individuals, and may also depend on the type of snus used, use time, and portion size.

- Intake (µg/day) = Concentration (µg/g dry weight) × (100 – moisture[b] (%))/100 × consumption (g/day). Intakes were presented as µg/day. When necessary, the daily intake can be converted to µg/kg body weight/day, by dividing with a body weight (b.w.), for example, 70 kg.

3.2 Approach to Estimate TSNA Exposure from Smoking

Estimates of intakes of TSNAs from smoking are based on smoking one pack of cigarettes per day (20 cigarettes) with 100% absorption from main stream smoke as well as with an adjusted absorption rate based on estimates from the scientific literature. Additional approaches are also briefly discussed. Appropriate average concentrations in main stream smoke for cigarettes used in the US were determined from the published literature with a focus on the most recent analyses.

3.3 Approach to Estimate HPHC Intakes from the Diet

The scientific literature and government agency reports were searched to identify population-based average dietary intakes. Where multiple values were identified, the more recent daily dietary intake values estimated by regulatory agencies were judged to be the most reliable information for the purpose, and more dated values were not used in this analysis. In addition to average intakes, attempts were made to identify a health-based guideline from regulatory and public health agencies, such as References Doses (RfDs) or Minimal Risk Levels (MRLs) from the USEPA or ATSDR. Where a recent, US-based value was available, no further attempts were made to identify values from other agencies. Where no US values were available,

[11] It should be noted that calculating dry weight to wet weight using (100 - water content (%) would result in slightly higher intake estimates: Water content was 5.2-9.3% lower than moisture.

guidelines obtained from international or European agencies such as JECFA or EFSA were used.

For HPHCs, where these dietary intakes and guideline values were not available, samples of concentrations in certain foods, including beverages, are provided to provide context to those concentrations in snus. These comparisons were given the least confidence, because consumption of specific foods is highly variable among individuals and likely not representative of the adult population, which limits the respective comparisons to average HPHC intakes.

4 Results

4.1 Available Data

Swedish Match analytical data was available for 40 of the 50 components from the FDA HPHC list that are considered potentially relevant for STPs and not purely combustion products. No data was available for nine PAHs and cobalt. The review of the scientific literature as presented in the ENVIRON Snus Monograph (2013) does not indicate that eight of these PAHs have been analyzed in STPs by other researchers (McAdam et al. 2010; Stepanov et al. 2010). Similarly, no data was available for cobalt. Although data for ammonia was available from Swedish Match it is not further discussed in the following sections, because the FDA list contains this HPHC for concerns about respiratory toxicity. Ammonia further impacts product pH and resulting nicotine delivery. These parameters are discussed in Section 2.3.3 of the ENVIRON Snus Monograph (2013).

In general, concentrations of the investigated HPHCs were similar for all the Swedish Match snus products presented here. Estimated intake differences largely result from varying moisture contents, portion sizes, and consumption patterns of the products.

4.2 Estimated Intakes of Alkaloids from Snus Consumption

The alkaloids anabasine and nornicotine are listed on the current FDA HPHC list for their addiction potential (FDA 2012). Nicotine is also listed for its addiction potential as well as for reproductive or developmental toxicity concerns. In addition to these alkaloids, Swedish Match analyzes anatabine in their products.

The concentrations of these alkaloids as measured in the eight snus products are presented in Table 1a in µg per g dry weight as well as per portion weight and per mg nicotine.

Table 1a: Alkaloids: Concentration in *General* Snus Brands

Analyte	Units	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Per dry weight									
Nicotine	mg/g dw	14	14	14	15	14	12	19	14
Anabasine	µg/g dw	79	70	62	68	59	52	130	64
Anatabine		230	250	230	230	210	190	510	200
Nornicotine		270	300	290	310	260	220	430	290
Per portion									
Nicotine	mg/portion	6.24	6.03	5.67	7.32	6.91	5.85	4.68	15.58*
Anabasine	µg/portion	35	30	25	33	29	25	32	71*
Anatabine		103	108	93	112	104	93	126	223
Nornicotine		120	47	44	50	42	34	106	41*
Per mg nicotine									
Anabasine	µg/mg nicotine	5.6	5.0	4.4	4.5	4.2	4.3	6.8	4.6
Anatabine		16.4	17.9	16.4	15.3	15.0	15.8	26.8	14.3
Nornicotine		19.3	21.4	20.7	20.7	18.6	18.3	22.6	20.7

PS: pouched snus; WL: white large; OL: original large; OM: original mini; dw: dry weight
* Assuming an average portion weight of 2.65 g for loose snus (Digard et al. 2009)

Intake Estimates from Snus Consumption

Table 1b summarizes the estimated alkaloid intakes. The average nicotine extraction from different snus products was reported to be 21 to 49% and was influenced by portion size, user experience, and usage time as well as by total nicotine content and pH (for more details see ENVIRON Snus Monograph (2013), Section 2.3.3).

The estimated intakes of nicotine, anabasine, and nornicotine from consumption of 12 g snus range from 68 to 88 mg/day for nicotine (or half that amount when the extraction is assumed to be approximately 50%), from 293 to 448 µg/day for anabasine, and from 1,238 to 1,815 µg/day for nornicotine for all pouched brands, except *General Dry Mint PSOM.*

For General Dry Mint PSOM, nicotine, anabasine, and nornicotine intakes from consumption of 12 g/day of the product are 169 mg/day, 1,154 µg/day, and 3,818 µg/day, respectively. When assuming consumption of 12 portions/day (0.33 g/portion) instead of 12 g/day, the estimated daily intakes are 56 mg/day, 385 µg/day, and 1,273 µg/day, respectively.

*For General Loose Snus, c*onsumption of 32 g/day results in estimated nicotine, anabasine, and nornicotine intakes of 188 mg/day, 860 µg/day and 3,898 µg/day, respectively.

Table 1b: Alkaloids: Estimated Daily Intakes from Consumption of *General* Snus Brands

Analyte	Units	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Nicotine	mg/d	80	79	77	88	81	67	169	188
	mg/d#	39	38	38	43	40	33	83	92
Anabasine	µg/d	448	394	342	398	343	293	1154	860
Anatabine		1306	1407	1270	1347	1220	1220	4529	2688
Nornicotine		1533	1688	1601	1815	1510	1238	3818	3898

PS: pouched snus; WL: white large; OL: original large; OM: original mini. All concentrations in dry weight
* based on a mean consumption of 12 g pouched snus, 32 g loose snus (12 portions/day) (Digard et al. 2009)
# Assuming 49% extraction

Worst Case - Alkaloids

For the worst case scenario calculation, maximum concentrations in Swedish Match snus brands from the 2011 Brand Testing data were available for all alkaloids per dry weight: nicotine (2.6% or 26 mg/g dry weight), anabasine (100 µg/g), anatabine (760 µg/g), and nornicotine (420 µg/g).

Using a 95th percentile consumption of 24 g/day pouched snus adjusted for the moisture of each individual product yields estimated maximum intake values up to 305 mg/day, 1171 and 4,919 µg/day for nicotine, anabasine, and nornicotine, respectively, for all pouched snus products except *General Dry Mint PSOM.*

*For General Dry Mint PSOM, u*sing a 95th percentile consumption of 24 g/day adjusted for the moisture content, estimated maximum intake values for nicotine, anabasine and nornicotine were 462 mg/day, 1776, and 7459 µg/day, respectively. When consumption of 24 portions/day is assumed instead of 24 g/day, the estimated maximum intake is 154 mg/day, 592 and 2,486 µg/day, respectively.

For General Loose Snus, using 95th percentile consumption of 77 g/day loose snus adjusted for the moisture content, the estimated maximum intake for nicotine, anabasine and nornicotine is 841 mg/day, 3234, and 13,583 µg/day, respectively.

4.3 Estimated Intakes of Tobacco-Specific *N*-Nitrosamines (TSNAs) from Snus Consumption – Comparison with Intakes from Smoking

The current FDA HPHC list contains NNK and NNN based on concerns about their carcinogenic potential (FDA 2012). Recently, the World Health Organization (WHO) Study Group on Tobacco Product Regulation, in its Report on the Scientific Basis of Tobacco Product Regulation, recommended that "the combined concentration of NNN plus NNK in smokeless tobacco should be limited to 2 µg/g dry weight of tobacco" (WHO 2009).

4.3.1 Estimated TSNA Intakes from Snus Consumption

Table 2a summarizes concentrations of NNN, NNK, NNN + NNK, and total TSNAs (NNN, NNK, NAB, and NAT) in the eight snus products. In addition to providing TSNA concentrations per g dry weight of tobacco, the concentrations are also presented as per portion size and per total nicotine content to account for differences in portion sizes, nicotine content and delivery (influenced by pH, e.g., the novel brand *General Dry Mint Mini* has a lower pH).

Note that NNN + NNK concentrations in the eight snus products were on average 0.86 µg/g dry weight (range, 0.67-1.03 µg/g dry weight) and therefore below the suggested WHO limit of 2 µg/g dry weight.

Table 2a: TSNAs: Concentrations in *General* Snus Brands

Analyte	Unit	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Per dry weight									
NNN	µg/g dw	0.60	0.59	0.56	0.79	0.58	0.58	0.59	0.44
NNK		0.33	0.30	0.27	0.24	0.29	0.29	0.21	0.23
Sum NNN+NNK		0.93	0.89	0.83	1.03	0.87	0.87	0.80	0.67
Sum TSNA¤		1.40	1.30	1.30	1.60	1.30	1.30	1.40	1.00
Per portion									
NNN	µg/ portion	0.27	0.25	0.23	0.39	0.29	0.28	0.15	0.49$^{\Delta}$
NNK		0.15	0.13	0.11	0.12	0.14	0.14	0.05	0.26$^{\Delta}$
Sum NNN+NNK		0.41	0.38	0.34	0.50	0.43	0.42	0.20	0.75$^{\Delta}$
Sum TSNA¤		0.62	0.56	0.53	0.78	0.64	0.63	0.34	1.1
Per mg nicotine									
NNN	µg/mg nicotine	0.04	0.04	0.04	0.05	0.04	0.05	0.03	0.03
NNK		0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.02
Sum NNN+NNK		0.07	0.06	0.06	0.07	0.06	0.07	0.04	0.05

PS: pouched snus; WL: white large; OL: original large; OM: original mini; dw: dry weight

Extraction

Extraction studies have shown that TSNA extraction varies significantly between individuals, depending on the type of snus used, usage time (also referred to as 'use time'), and portion size (based on data for nicotine extraction). Several studies were available in which TSNA extraction was measured under controlled study conditions using a 1-g snus in pouched portions. For 30 minutes use time, extraction rates for various Swedish Match products were reported to range from 14 and 41% in one study (SM WS-03) and the mean extraction rate was 18% in another study with different snus products (Gale et al. 2011). For 60 minutes use time, mean TSNA extraction rates ranged from 30% to 36% (Digard et al. 2013; Gale et al. 2011), and up to 49% of TSNAs were extracted after 120 minute use time (Gale et al. 2011). Extraction of individual TSNAs appeared to be similar to each other (Digard et al. 2013). Under free 24-hour use conditions, TSNA extraction from traditional Swedish snus averaged to 57% and 64% for pouched and loose snus, respectively (Andersson et al. 1994). Other researchers have used 60% extraction of TSNAs from STPs (Hecht et al. 2008). It should be noted that recent studies tested pouched traditional Swedish snus products, and did not include loose snus or novel products, such as *General Dry Mint Mini*.

Therefore, a 40% extraction rate of TSNAs for 30 to 60 minute use times was used to estimate TSNA intakes from snus consumption, and the worst case scenario used an estimate of 60% extraction rate. Since no absorption studies with traditional Swedish snus were available, absorption of TSNAs from snus was assumed to be 100%.

Intake Estimates

Table 2b summarizes the estimated intakes in three ways; before extraction is taken into consideration and with 40% extraction as µg TSNAs per day, and presented as µg per kg body weight per day using the 40% extraction assumption.

<u>NNN</u>

Using 40% extraction, the estimated NNN intake from consumption of 12 g snus is highest for *General PSOL* with 1.9 µg/day and ranges minimally for all other pouched brands, from 1.2-1.4 µg/day, with the exception of *General Dry Mint PSOM.*

For *General Dry Mint PSOM,* NNN intake from consumption of 12 g/day is estimated to be 2.1 µg/day. When consumption of 12 portions/day (0.33 g/portion) is assumed instead, the estimated daily intake is 0.7 µg/day.

Daily consumption of 32 g of *General Loose Snus* results in an estimated NNN intake of 2.4 µg/day.

<u>NNK</u>

The estimated NNK intake from consumption of 12 g snus ranges from 0.56-0.75 µg/day for all pouched brands.

NNK intake from *General Dry Mint PSOM* consumption of 12 g/day is calculated to be 0.75 µg/day. When consumption of 12 portions/day (0.33 g/portion) is assumed instead of 12 g/day, the estimated daily intake is 0.25 µg/day.

Consumption of 32 g of *General Loose Snus* results in an estimated NNK intake of 1.24 µg/day.

Table 2b: TSNAs: Estimated Daily Intakes from Consumption of *General* Snus Brands

Analyte	Unit	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Assuming 100% extraction									
NNN	µg/d	3.41	3.32	3.09	4.63	3.37	3.37	5.24 (1.74)**	5.91
NNK		1.87	1.69	1.49	1.41	1.68	1.68	1.86 (0.62)**	3.09
Sum TSNA		7.95	7.32	7.18	9.37	7.55	7.32	12.43 (4.14)**	13.44
Assuming 40% extraction									
NNN	µg/d	1.36	1.33	1.24	1.85	1.35	1.35	2.10 (0.7)**	2.37
NNK		0.75	0.68	0.60	0.56	0.67	0.67	0.75 (0.25)**	1.24
Sum TSNA		3.18	2.93	2.87	3.75	3.02	2.93	4.97 (1.66)**	5.38
Assuming 40% extraction and 70 kg body weight									
NNN	µg/kg/d	0.019	0.019	0.018	0.026	0.019	0.019	0.030 (0.010)**	0.034
NNK		0.011	0.010	0.009	0.008	0.010	0.010	0.011 (0.004)**	0.018
Sum TSNA		0.045	0.042	0.041	0.054	0.043	0.042	0.071 (0.024)**	0.077

PS: pouched snus; WL: white large; OL: original large; OM: original mini; dw: dry weight;
* based on a mean consumption of 12 g pouched snus, 32 g loose snus (12 portions/day) (Digard et al. 2009)
** based on mean loose snus consumption of 12 portions/day instead of 12 g/day
$^{\Delta}$ based on a mean portion size of 2.65 g loose snus (Digard et al. 2009)

Total TSNAs - Worst Case

For the worst case scenario calculation, a maximum concentration in Swedish Match snus brands was available only for total TSNAs (2.3 µg/g) from the Brand Testing data and not for NNN or NNK.

Using a 95th percentile consumption of 24 g/day snus adjusted for the moisture of each individual product yields estimated maximum intake value up to 16 µg/day assuming 60% extraction for total TSNAs for all pouched snus products except *General Dry Mint PSOM.*

For *General Dry Mint PSOM*, using a 95th percentile consumption of 24 g/day adjusted for moisture yields an estimated maximum intake value of 24 µg/day total TSNAs when assuming 60% extraction. When consumption of 24 portions/day is assumed instead, the estimated maximum intake is 8.4 µg/day total TSNAs when assuming 60% extraction.

For *General Loose Snus,* using 95th percentile consumption of 77 g/day loose snus adjusted for moisture yields an estimated maximum intake value of 44 µg/day total TSNAs when assuming 60% extraction.

By comparison, the average estimated intake from any of the eight products is up to 5.4 µg/day total TSNAs, assuming 40% extraction (8.1 µg/day assuming 60% extraction).

4.3.2 Estimated Exposure from Smoking and Comparison with Intakes from Snus

TSNA concentrations in mainstream smoke of 90 different cigarette brands smoked under the ISO/FTC smoking regimen as reported in analyses from 2010 to 2012 were extracted from the review by Appleton and colleagues (2013). The average (arithmetic mean) for this data set was calculated for NNN, NNK, and total TSNAs (available from Stepanov et al. 2012a) for a subset of the data) (Table 2c). Since the ISO/FTC smoking regimen is thought to underestimate real-life smoking, TSNA concentrations were also adjusted based on an analysis by Djordjevic and colleagues (2000) that observed a ratio of 1.7 for measured/FTC concentrations. For simplified estimates, 100% absorption of the concentrations in mainstream smoke is assumed. Alternatively, some authors have reported mouth level exposures (MLE, the smoke portion drawn into the front of the mouth) (Ashley et al. 2010). A comparison of the reported MLEs for smoking 15 to 17 cigs/day with the intakes calculated based on mainstream smoke concentrations show that they are in the same range as the adjusted average calculated for smoking 20 cigs/day (see Table 2c). St. Charles and colleagues (2013) reported that on average 35% of the smoke entering the mouth is not inhaled. Thus, assuming 100% absorption is likely an overestimate of exposure to constituents in smoke (see Table 2c). Accordingly, intake estimates were compared either assuming 100% extraction/absorption for both snus and smoking or, as adjusted, with the assumed extraction rates for snus and 65% absorption from smoking.

Table 2c: TSNA Concentrations in Main Stream (MS) Smoke and Estimated Daily Exposure from Smoking

	NNN	NNK	TSNAs
Average concentration in MS smoke - ISO/FTC (μg/cigarette)	0.088*	0.057*	0.333**
Adjusted average concentration in MS smoke (μg/cig) §	0.149	0.096	0.565
Exposure from smoking 20 cigs/day based on unadjusted FTC MS smoke concentrations (μg/day) assuming 100% absorption	1.75	1.13	6.65
Exposure from smoking 20 cigs/day based on adjusted FTC MS smoke concentrations (μg/d) assuming 100% absorption	2.98	1.93	11.31
Exposure assuming 65% absorption ¥	1.94	1.25	7.35
Mouth level (ML) exposure from smoking 15-17 cig/day (μg/day)***	2.51-3.14	1.15-1.49	NR
ML Exposure assuming 65% absorption ¥	1.63-2.04	0.75-0.97	NR

* Averages calculated based on data reported for 2010-2012 in Appleton et al. 2013
** Data from Stepanov et al. 2012
§ based on Djordjevic et al. 2000 (ratio of 1.7 for measured/FTC concentrations to adjust for real-life smoking)
¥ based on St. Charles et al. 2013
*** US (New York and MN) data from Ashley et al. 2010

NNN and NNK

When estimated NNN and NNK intakes from smoking are compared with those from consumption of 12 g of pouched products (using 12 portions for *General Dry Mint PSOM),* NNN intakes were generally the same, and NNK intakes were the same or somewhat lower when either 100% or 40/65% extraction/absorption is assumed for both tobacco products and compared. The intake estimate based on consumption of 32 g of *General Loose Snus* is up to two times higher assuming 100% absorption, but is similar to that of smoking when the extraction/absorption values are taken into account for the estimates of both snus and smoking.

Total TSNAs – Worst Case

For the worst case scenario, consumption of 24 g/day of all pouched products (using 24 portions/day for *General Dry Mint PSOM* and otherwise as described above, assuming 60% extraction) results in estimated TSNA intakes that are lower than those resulting from smoking 40 cigarettes (39 μg/day or 25 μg/day assuming 100 or 65% absorption, respectively, with 0.575 μg/cig maximum concentrations in main stream smoke under FTC conditions (Stepanov et al. 2012a), adjusted to 0.972 μg/cig) with or without accounting for absorption differences. Consumption of 77 g/day loose snus results in estimated TSNA intakes that are comparable to smoking 75 cigarettes (73 μg/day or 47 μg/day assuming 100 or 65% absorption, respectively).

Estimated Intake Comparisons from the Published Literature

In a recent review, Nilsson (2011) calculated the daily total uptakes of NNN and NNK from Swedish snuff with average concentrations of 0.96 and 0.32 μg/g, respectively, citing concentrations of these components from Österdahl and colleagues (2004). Using a daily consumption value of 20 g snuff, 70 kg body weight, and a 60% absorption rate, NNN and NNK intake were estimated to be 0.082 and 0.027 μg/kg/day, respectively. These estimated intakes

are similar to those calculated in the present analysis for consumption of 32 g of *General Loose Snus* using an assumed absorption rate of 60%: 3.55 µg/day (5.91 µg/day x 0.6) or 0.051 µg/kg/day NNN and 1.85 µg/day (3.09 µg/day x 0.6) or 0.026 µg/kg/day NNK.

To compare the intake estimates with those from smoking, the intake from smoking 20 cigarettes was calculated based on average yields in mainstream smoke reported by Harris and colleagues (Harris et al. 2004 as cited in Nilsson 2011) and assuming 100% absorption in the lung. With 0.17 µg NNK and 0.25 µg NNN per cigarette, daily intakes were calculated to be 0.05 µg/kg/day NNK and 0.07 µg/kg/day NNN (Nilsson 2011). Based on these estimates, NNK and NNN intakes from snus use were in a similar range as those from smoking, with slightly lower NNK intakes from snus. Therefore, while the concentrations were higher for both mainstream smoke and snus, intake estimates were comparable in a similar manner as those calculated with newer analytical data in the present report.

4.3.3 Published Risk Assessments for TSNAs in Snus

Two assessments of potential cancer risk from TSNAs in STPs, including “Swedish snus”, have been published (Ayo-Yusuf and Connolly 2011; Haussmann 2012). In addition, two studies directly compared estimated TSNA intakes by humans from use of tobacco products with doses that caused tumors in rats (Balbo et al. 2013; Hecht et al. 2008).

Ayo-Yusuf and Connolly 2011

As described also in Section 2.3.6 of the ENVIRON Snus Monograph (2013), Ayo-Yusuf and Connolly (2011) used a TD_{50} value of 0.0999 mg/kg/day, as provided in the Carcinogenic Potency Database of the University of California at Berkeley (CPDB) , based on development of tumors in rat lung, liver, and pancreas after chronic administration of NNK via drinking water, to calculate the cancer risk estimate for the total TSNA exposure from STPs. NNK is only one of the components of total TSNAs, and though the CPDB reported that the TD_{50} for NNN was similar for NNK, Haussmann (2012) pointed out that according to oral cancer slope factors (based on animal studies) listed by CalEPA, NNK is significantly (35 times) more potent than NNN. Similarly, there is no basis to assume the same cancer risk for NAB and NAT. An additional limitation of the Ayo-Yusuf and Connolly analysis is that they made no adjustments for interspecies extrapolations and used TD_{50} values from animal experiments directly ($1/TD_{50}$) as carcinogenic potency factors (Ayo-Yusuf and Connolly 2011).

The Ayo-Yusuf and Connolly (2011) estimate of total TSNA intake, 19.63 µg/day (2.309 x 10 x 0.85) or 0.28 µg/kg/day total from “Swedish snus” consumption, was based on the concentration of TSNAs provided by Rickert and colleagues (2009) for *Du Maurier* snus (2.309 µg/g dry weight), which is not a traditional Swedish snus product, a daily use of 10 g dry weight, and a bioavailability of 85%. By comparison, in the present analysis, total TSNA intake resulting from consumption of 32 g (wet weight) of *General Loose Snus*, even with an assumption of 85% bioavailability, would result in only approximately half of the intake as estimated by Ayo-Yusuf and Connolly (2011): 11.42 µg/day (13.44 µg/d x 0.85) or 0.16 µg/kg/day. This difference is due to a lower concentration of TSNAs in the eight Swedish Match snus products discussed here.

Ayo-Yusuf and Connolly (2011) estimated the average lifetime daily exposure using the TSNA concentrations multiplied by the average daily use of snus (10 g/day dry weight), for 30 years of

use, over a total of 70 years average lifetime, for 70 kg body weight (0.28 μg/kg/day x30/70 = 0.12 μg/kg/day).

The resulting "reduced transfer" (assuming 85% bioavailability) cancer risk was calculated to be 1.2 $x10^{-3}$ (0.00012 mg/kg/d x 0.85 x 1/0.0999 = 0.00102 or 1.02 x 10^{-3}).

Haussmann 2012

Haussmann (2012) recalculated the theoretical incremental lifetime cancer risk (ILCR) for both NNK and NNN based on their assumed contributions in STPs meeting the GOTHIATEK® Standard limit assuming 85% bioavailability, and using oral cancer slope factors from CalEPA. Therefore, his estimate is for an STP containing a concentration of 10 μg/g dry weight total TSNAs, and an assumed average contribution of 15% NNK and 46% NNN to the total TSNA content.[12] Oral cancer slope factors from CalEPA were 49 and 1.4 $(mg/kg/day)^{-1}$ for NNK and NNN, respectively.[13] The resulting theoretical ILCRs for a STP containing 1.5 μg/g dry weight NNK and 4.6 μg/g dry weight NNN were 3.8 $x10^{-3}$and 3.4 $x10^{-4}$, respectively. Based on his calculation of ILCRs for five other components, Haussmann (2012) attributed a relative contribution to the total ILCR of 90% to NNK and 8% to NNN.

It should be noted that the above component-based type risk assessments have many limitations. For example, whole mixture effects, such as potential combination effects and interactions, are not taken into account. Haussmann (2012) concluded that "Within the scope of applying the hazard index concept to smokeless tobacco and among those constituents selected for analysis by these authors,[55] [Ayo-Yusuf and Connolly 2011] NNK may be the sole constituent with relevant contribution. Nevertheless, this theoretical evaluation per se does not confirm any actual role of NNK in smokeless tobacco-related disease pathogenesis. For the judgment of this relationship, all available epidemiological and mechanistic information needs to be considered."

In fact, in a recent review and analysis of published data of DNA and hemoglobin adducts in human and animal tissues by Nilsson (2011), this author concluded that "[w]hereas smoking and use of snuff [Swedish snus] result in similar exposures to the systemic carcinogens NNK and NNN, only smoking is associated with human lung cancer. This observation gives further support to the notion that TSNA probably play a minor role in the induction of smoking-related cancers." (see additional discussion in ENVIRON Snus Monograph (2013), Section 3.2.1.1.).

Hecht and Colleagues 2008

Hecht and colleagues (2008) estimated NNK intake for traditional US-type STPs to be approximately 6 μg/day (under the assumptions of an exposure to approximately 10 μg/day (0.5 μg/g wet weight tobacco, 20 g/day STP consumption and based on a 59% extraction rate)). They estimated that the accumulated intake of NNK to a daily user over 20 years was thus 44 mg or 0.6 mg/kg (70 kg body weight). The authors concluded that "[t]his is ~60 times less than the total dose of NNK that induced a significant incidence of lung and pancreatic tumors in rats

[12] It should be noted that both NNK and NNK ratios to total TSNAs can vary depending on the product. In the 8 snus products discussed in the present analysis, NNN constitutes the highest proportion (42-49%) of total TSNAs, followed by NAT, NNK (15-24%) and NAB. .

[13] For NNK, based on all cancers (CalEPA 2001)

when given chronically in the drinking water […].” These authors considered this “[…] a minimal safety margin when one considers that smokeless tobacco products also contain *N'*-nitrosonornicotine, an esophageal carcinogen, usually in amounts 3 to 10 times greater than NNK (12)” (see below).

By comparison, average NNK intake estimates adjusted for 40% extraction as calculated in the present analysis ranged from 0.56-0.75 µg/day µg/day (for 20 years of use: 4.09-5.48 mg, 0.058-0.078 mg/kg b.w) for the 1-g pouched snus products and 1.24 µg/day (for 20 years of use: 9.05 mg, 0.129 mg/kg b.w) for the loose snus product, 5 to 11 times less than in the above calculation by Hecht and colleagues (2008).

Balbo and Colleagues 2013

In a more recent study, researchers from the Hecht group (Balbo et al. 2013) showed that the *S*-enantiomer of NNN is the main oral and esophageal cancer-causing agent, while the *R*-enantiomer did not cause a significant increase in cancer incidence when administered in drinking water. These authors estimated human exposure to NNN from consumption of half a tin (17 g)/day) of “a popular smokeless tobacco product” to be 31 µg/day (3 µg/g wet weight, 60% extraction efficiency) or 339 mg (4.84 mg/kg b.w.) total intake for 30 years of use. They compared this to the daily NNN dose in the animal studies, in which 280 µg/day and total dose of 234 mg (352 mg/kg b.w.) caused oral cavity and esophageal tumors in all exposed male F344 rats by 17 months of exposure. A total dose of *S*-NNN 123 mg (336 mg/kg b.w.) also induced these tumors in all exposed rats. They noted that “[i]t is unclear whether a body weight correction is relevant considering that smokeless tobacco is concentrated in the oral cavity and frequently held at one site.”

Balbo and colleagues (2013) concluded that “the results of this study provide a previously unrecognized and critical link between a tobacco constituent and oral cavity cancer in tobacco users […]”. Though they further state that cigarette smoking and “smokeless tobacco” are established causes of oral cavity cancer (Balbo et al. 2013), the same is not the case for Swedish snus.

By comparison, average NNN intake estimates adjusted for 40% extraction as calculated in the present analysis ranged from 1.24-1.85 µg/day (for 30 years of use: 13.6-20.3 mg, 0.19-0.29 mg/kg b.w) for the 1-g pouched snus products and 2.37 µg/day (for 30 years of use: 26.0 mg, 0.37 mg/kg b.w) for the loose snus product. Based on an estimated 66% *S*-NNN of the NNN concentration as determined in a study by Stepanov and colleagues (2012b) in novel STPs (but not including traditional Swedish snus), the average total intake of *S*-NNN for using 32 g of *General Loose Snus* for 30 years would be 17.1 mg (0.24 mg/kg b.w; 26 mg x 0.66). This is seven times less than the total *S*-NNN dose in rats as described above (Balbo et al. 2013). In addition, differences between rats and humans, e.g. in activation metabolism of NNN, as well as potential interactions with other tobacco components, may contribute to the inconsistencies in observed cancer incidence in animal studies compared to the findings from numerous epidemiological studies among users of Swedish snus.

4.3.4 Summary

The present analysis was conducted to inform "the health risk associated with use of the proposed MRTP as compared to using other tobacco products on the market […]", i.e., smoking [part A], assuming that a similar exposure to a component might result in a similar risk. The results demonstrate that on average and under worst case conditions, the intakes of NNN and NNK as well as total TSNAs from snus consumption and smoking are comparable. However, there is no clear evidence from epidemiological studies of human snus consumption of increased cancer incidence at sites judged "positive" in the animal studies of TSNAs, and findings from the epidemiology studies are not consistent with the chemical-specific risk assessments that use data from the latter studies to estimate excess cancer risks.

4.4 Estimated Intakes of HPHCs (except Alkaloids and TSNAs) – Comparison with Intakes from the Diet

Estimates of intakes from snus consumption were calculated for the remaining HPHC components/component classes, i.e., other *N*-nitrosoamino acids, volatile *N*-nitrosamines (VNAs), *N*-nitrosodiethanolamine (NDELA), PAHs, aldehydes, metals and metalloids, radioisotopes, acrylamide, aflatoxin, and ethyl carbamate (urethane). These were then compared to estimates of dietary intake and guideline values for oral intake as available from regulatory health agencies. Where these intake values were not available, alternatively, concentrations in foods were identified from the published literature. Because the objective was to compare intake of HPHCs from snus with that from the diet (foods), more recent daily dietary intake values estimated by regulatory agencies were judged to be most reliable information for the purpose. A comparison with guideline values were provided where the information was available. The least confidence was given in comparisons with concentrations in diverse foods.

Limitations of the Approach

The above described comparisons with intake from food, assume similar extraction and uptake of the HPHCs from food and snus, which is likely not the case. Unlike food, snus is not swallowed, and thus does not undergo the complete digestion cycle. For snus, only the amount of components extracted is available for absorption. This extraction process takes place in the oral cavity and the main routes of absorption for components from snus are through the oral mucosa or through absorption from swallowed saliva in the gastrointestinal tract. This is different from most foods where the main part of extraction and absorption will take place in the gastrointestinal tract.

Therefore, even though extraction data can contribute to a more accurate estimate of the actual HPHC intake from snus consumption, the direct absorption would likely differ from that from foods. The effect of differences in the route of exposure from snus compared to diet on internal/systemic exposure may be estimated by comparison of appropriate biomarkers of exposure.

Any comparison of intakes from snus versus diet will not be able to account for potential local effects on the oral mucosa. These may be best determined in clinical and/or epidemiological studies.

4.4.1 *N*-Nitroso Compounds Other than TSNAs

4.4.1.1 *N*-Nitrosamino Acids

The current FDA HPHC list contains *N*-nitrososarcosine (NSAR) categorized based on its carcinogenic potential (FDA 2012).

Table 3a summarizes the concentrations detected in the eight snus products.

Table 3a: NSAR: Concentrations in *General* Snus Brands and Estimated Daily Intakes from Consumption of *General* Snus Brands

NSAR	Units	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Concentration	ng/g dw	19.90	49.80	22.60	15.30	20.70	20.60	<0.784	19.10
Daily intake	µg/day	0.11	0.28	0.12	0.09	0.12	0.12	0.0049[¥]	0.26

PS: pouched snus; WL: white large; OL: original large; OM: original mini.; dw: dry weight
[¥] Intake estimates from concentrations <LOD

Intake Estimates from Snus Consumption

Table 3a also summarizes the estimated NSAR intakes (concentrations below LOD or LOQ were calculated as described under Section 3.1 assuming 100% extraction). No other extraction information was available.

The estimated NSAR intake from consumption of 12 g snus is in the range of 0.0049 and 0.28 µg/day for all pouched brands.

Consumption of 32 g of *General Loose Snus* results in an estimated NSAR intake of 0.26 µg/day.

<u>NSAR – Worst Case</u>

A maximum concentration of NSAR (26.3 ng/g) in Swedish Match snus brands was available from the Brand Testing data.

Using a 95th percentile consumption of 24 g/day snus adjusted for the moisture of each individual product yields estimated maximum intake value up to 0.31 µg/day for NSAR for all pouched snus products except *General Dry Mint PSOM.*

Using a 95th percentile consumption of 24 g/day adjusted for the moisture of *General Dry Mint PSOM* yields an estimated maximum intake value of 0.47 µg/day for NSAR. Assuming consumption of 24 portions/day, the estimated maximum intake is 0.16 µg/day.

Using 95^{h} percentile consumption of 77 g/day loose snus adjusted for the moisture of *General Loose Snus* yields an estimated maximum intake value of 0.85 µg/day for NSAR.

Comparison with Intake from Dietary Sources

Little information with respect to sound dietary intake values of NSAR was available. Using a comparison to the concentration found in foods, the estimated daily intake of NSAR from snus consumption is, even under the worst case scenario, within the range of amounts that may be ingested from consumption of 50 g smoked meat (NTP 2011; see Table 3d).

4.4.1.2 Volatile *N*-Nitrosamines (VNAs)

The current FDA HPHC list contains six VNAs: *N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosomethylethylamine (also sometimes as N-nitrosoethylmethylamine, NEMA), *N*-nitrosomorpholine (NMOR), *N*-nitrosopyrrolidine (NPYR), and *N*-nitrosopiperidine (NPIP) based on concerns about their carcinogenic potential (FDA 2012).

In addition to these six components, Swedish Match also measured four other VNAs (*N*-nitrosodibutylamine (NDBA), *N*-nitrosodi-n-propylamine (NDPA), *N*-nitrosodiisopropylamine (NDiPA, and *N*-nitrosodiisopropanolamine (NDIPLA).

Of the ten VNAs, six were not detected (below their respective LODs) in any of the eight products: three HPHC-list VNAs (NDEA, NEMA and NPIP) as well as NDBA, NDPA and NDiPLA.

Three of the remaining VNAs were detected in a few products but not quantifiable (NQ; below their respective LOQ), except for NMOR:

- in *General Loose Snus* – NMOR was 5.1 ng/g dry weight, NPYR and NDiPA were NQ
- in *General PSOL* – NPYR and NMOR were NQ, and
- in *General Mint* PSWL – NMOR was NQ.

NDMA was not detected in measurements by LabStat, but detected in two products in the Swedish Match Chemical Laboratory (CAS):

- *General PSWL* at 0.8 ng/g dry weight and
- *General Wintergreen* at 1.1 ng/g dry weight.

Intake Estimates from Snus Consumption

Table 3b summarizes the estimated VNA intakes (concentrations below LOD or LOQ were calculated as described under Section 3.1) assuming 100% extraction. No other extraction information was available.

The estimated NDMA intakes from consumption of 12 g pouched snus brands or 32 g *General Loose Snus* range from 0.0023 to 0.0062 µg/day (calculated based on concentrations that were below the LOD for all but two products).

The estimated intakes for all other individual VNAs (calculated based on concentrations that were below their respective LOD or LOQ) from consumption of 12 g snus range from 0.0021 to 0.0095 µg/day, for all pouched brands, except *General Dry Mint PSOM.*

Estimated intakes of all other individual VNAs from *General Dry Mint PSOM* consumption of 12 g/day range from 0.0036 to 0.0144 µg/day. When consumption of 12 portions/day (0.33 g/portion) is assumed instead, the estimated daily intakes are in the range 0.0012 to 0.0048 µg/day.

Consumption of 32 g of *General Loose Snus* results in an estimated intake of individual VNAs in the range of 0.0057 to 0.0526 µg/day (calculated based on concentrations that were below their respective LOD or LOQ), 0.0685 µg/day NMOR, and a total VNA intake of 0.23 µg/day (summing intakes for all 10 VNAs measured by Swedish Match, and using calculated concentrations below the LOD or LOQ).

Table 3b: VNAs: Estimated Daily Intakes from Consumption of *General* Snus Brands (µg/day)

Analyte	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
	4352	4876	4877	4880	4881	4882	4800	4852
NDMA¤	0.0024¥	0.0024¥	0.0023¥	0.0025¥	0.0046	0.0062	0.0038¥	0.0057¥
NDEA	0.0056¥	0.0056¥	0.0055¥	0.0058¥	0.0057¥	0.0056¥	0.0088¥	0.0133¥
NEMA	0.0054¥	0.0054¥	0.0053¥	0.0056¥	0.0055¥	0.0054¥	0.0085¥	0.0128¥
NMOR	0.0071‡	0.0021¥	0.0021¥	0.0073‡	0.0022¥	0.0021¥	0.0033¥	0.0685
NPYR	0.0067¥	0.0066¥	0.0065¥	0.0229‡	0.0068¥	0.0066¥	0.0104¥	0.0526‡
NPIP	0.0092¥	0.0091¥	0.0089¥	0.0095¥	0.0094¥	0.0091¥	0.0144¥	0.0218¥
NDBA*	0.0085¥	0.0084¥	0.0082¥	0.0087¥	0.0087¥	0.0084¥	0.0132¥	0.0201¥
NDPA*	0.0061¥	0.0060¥	0.0059¥	0.0063¥	0.0062¥	0.0060¥	0.0095¥	0.0144¥
NDiPLA*	0.0026¥	0.0026¥	0.0025¥	0.0027¥	0.0026¥	0.0026¥	0.0040¥	0.0061¥
NDiPA*	0.0023¥	0.0023¥	0.0023¥	0.0024¥	0.0024¥	0.0023¥	0.0036¥	0.0183‡

PS: pouched snus; WL: white large; OL: original large; OM: original mini.
* Not on FDA HPHC List
¥ Intake estimates from concentrations <LOD
‡ Intake estimates from concentrations <LOQ

VNAs - Worst Case

For the worst case scenario calculation, a maximum concentration in Swedish Match snus brands was available only for NDMA (3.7 ng/g) from the Brand Testing data.

Using a 95th percentile consumption of 24 g/day pouched snus adjusted for the moisture of each individual product yields estimated maximum intake values up to 0.04 µg/day for NDMA for all pouched snus products except *General Dry Mint PSOM.*

For *General Dry Mint PSOM,* using a 95th percentile consumption of 24 g/day adjusted for its moisture content, yields an estimated maximum intake value of 0.07 µg/day NDMA. When

consumption of 24 portions/day is assumed instead, the estimated maximum intake is 0.02 µg/day.

Using 95 [h] percentile consumption of 77 g/day loose snus adjusted for the moisture of *General Loose Snus* yields an estimated maximum intake value of 0.12 µg/day for NDMA.

Comparison with Intake from Dietary Sources

For most of the VNAs, little information with respect to sound dietary intake values was available. Where data was available for concentrations in foods, comparison with the estimated VNA intakes from snus consumption indicates that these are generally below or similar to intakes that could result from consumption of certain foods (see Table 3d).

Estimated intakes for NDMA even under worst case scenario conditions are below the range of the estimated combined intake of NDMA from air, water, and food (WHO 2002).

The estimated intake of total VNAs (summing the 10 VNAs measured by Swedish Match) from 32 g of *General Loose Snus,* presenting the highest average intake, is 0.23 µg/day and similar to the reported average dietary intake of total VNAs (NDMA, NDBA, NPIP, and NPYR) of 0.29 µg/day (Österdahl 1988; Österdahl 1991).

4.4.1.3 *N*-Nitrosodiethanolamine (NDELA)

NDELA is on the current FDA HPHC list based on concerns about its carcinogenic potential (FDA 2012).

Table 3c summarizes the concentrations detected in the eight snus products.

Table 3c: NDELA: Concentrations in *General* Snus Brands and Estimated Daily Intakes from Consumption of *General* Snus Brands

NDELA	Units	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Concentration	ng/g dw	400.4	199.2	307.5	275.9	231.3	256.2	156.8	307.4
Daily intake	µg/d	2.27	1.12	1.70	1.62	1.34	1.44	1.39	4.13

PS: pouched snus; WL: white large; OL: original large; OM: original mini; dw: dry weight

Intake Estimates from Snus Consumption

Table 3c summarizes the estimated NDELA intakes (concentrations below LOD or LOQ were calculated as described under Section 3.1) assuming 100% extraction. No other extraction information was available.

The estimated NDELA intake from consumption of 12 g pouched snus is in the range of 1.12 and 2.27 µg/day for all pouched brands.

Consumption of 32 g of *General Loose Snus* results in an estimated NDELA intake of 4.13 µg/day.

Worst Case -NDELA

A maximum concentration of NDELA (37.2 ng/g dry weight) in Swedish Match snus brands was available from the 2011 Brand Testing data. The concentrations reported in 2011 by the contracting LabStat were significantly lower than those reported in 2012. However, 2013 concentrations were reported to be lower again. The latter changes were attributed to a change in analytical methods by the contract laboratory, but do not explain the discrepancy between the data from 2011 and 2012 (Johan Lindholm, Swedish Match, personal communication). There is only limited published data reporting NDELA concentrations in Swedish snus between 225 to 390 ng/g dry weight in the 1980s, 8 to 31 ng/g (unspecified if per wet or dry weight) in 1991 and below the LOD of 0.78 ng/g wet weight in 2010 (see *ENVIRON Snus Monograph (2013)*, Section 2.3.6.1). It is thought that concentrations have decreased with the gradual agronomic reduction of maleic hydrazide-diethanolamine as a sucker growth-controlling agent (IARC 2007). Therefore, it appears that the 2012 data is in a similar range as concentrations reported in the 1980s and it can be assumed to represent a worst case scenario. The highest concentration in the eight products was 400.4 ng/g dry weight.

Using this concentration and a 95th percentile consumption of 24 g/day pouched snus adjusted for the moisture of each individual product yields estimated maximum intake value up to 4.7 µg/day (instead of 0.44 µg/day based on 2011 Brand Testing maximum concentrations) for NDELA for all pouched snus products except *General Dry Mint PSOM.*

Using a 95th percentile consumption of 24 g/day adjusted for the moisture of *General Dry Mint PSOM* yields an estimated maximum intake value of 7.1 µg/day (instead of 0.66 µg/day based on 2011 Brand Testing maximum concentrations) for NDELA. When consumption of 24 portions/day was assumed, the estimated maximum intake was 2.4 µg/day (instead of 0.22 µg/day).

Using a 95th percentile consumption of 77 g/day loose snus adjusted for the moisture of *General Loose Snus* yields an estimated maximum intake value of 13 µg/day (instead of 1.2 µg/day based on 2011 Brand Testing maximum concentrations) for NDELA.

Comparison with Intake from Dietary Sources

No information with respect to reliable dietary intake values of NDELA and only little information regarding concentrations in foods were available. The highest average estimated NDELA intake from consumption of 32 g *General Loose Snus* is within the range of intakes that may result from consumption of a few grams of cured meat (under worst case conditions consumption of 15 g of such meat) (IARC 2000; see Table 3d).

Table 3d: *N*-Nitroso Compounds: Concentrations in Foods and Estimated Dietary Intakes

***N*-Nitroso Compound**	**IARC Group**	**Concentrations in Food**
		***N*-Nitrosamino Acids**
N-Nitrososarcosine (NSAR)	2B	2 to 56 µg/kg in smoked meat (NTP 2011)
		Volatile *N*-Nitrosamines
N-Nitrosodiethylamine (NDEA)	2A	0.5-147 µg/kg in soybeans and oil, cured meat and alcoholic beverages. High concentration in salt-dried fish at 1.2 to 21 mg/kg (NTP 2011)
N-Nitrosodimethylamine (NDMA)*	2A	2.7 µg/kg in fried bacon, 0.23-0.93 µg/kg in edible oils, 0.3 µg/kg in margarine, traces in cheese, 1.2 µg/kg in whole wheat biscuits, 0.8 µg/kg in flour, 0.8 µg/kg in dried peas, 0.4 µg/kg in malt vinegar, 0.54 µg/kg in prosciutto, 5.35 µg/kg in salami, and 0.84 µg/kg in gorgonzola (HSDB 2010). Estimated dietary intake for the age group of 20-59 years was 0.005-0.016 µg/kg/d (based on data that are limited in both spatial and temporal scope, reference values for body weight, and combined intake from air, water and food). Intakes as high as 0.03 µg/kg/d (WHO 2002).
N-Nitrosomethylethylamine (NEMA)	2B	No data
N-Nitrosomorpholine (NMOR)	2B	No data
N-Nitrosopyrrolidine (NPYR)	2B	17 µg/kg in 1975-76 bacon content (NTP 2011)
N-Nitrosospiperidine (NPIP)	2B	Up to 64 µg/kg in meat and fish products such as bacon, bologna, wieners, and smoked cod (NTP 2011)
		Non-volatile *N*-Nitrosamines
N-Nitrosodiethanolamine (NDELA)	2B	Dairy products in Nigeria: 1.5-7 µg/kg; Meat: 0.87-1.89 mg/kg (IARC 2000).

* GOTHIATEK® Standard limits established.

4.4.2 Polycyclic Aromatic Hydrocarbons (PAHs)

The HPHC list of the FDA currently contains 17 PAHs (Benz[*a*]anthracene (B[*a*]A), benz[*j*]aceanthrylene, benzo[*b*]fluoranthene (B[*b*]F, benzo[*k*]fluoranthene (B[*k*]F, benzo[*b*]furan, benzo[*a*]pyrene (B[*a*]P), benzo[*c*]phenanthrene, chrysene, cyclopenta[*c,d*]pyrene, dibenz[*a,h*]anthracene (D[*a,h*]A), dibenzo[*a,e*]pyrene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, dibenzo[*a,l*]pyrene, indeno[*1,2,3-cd*]pyrene (I[*1,2,3-cd*]P), 5-methylchrysene, and naphthalene) based mostly over concerns about their carcinogenic potential (FDA 2012). For eight of these PAHs (not underlined), data for concentrations in STPs were neither available in the published literature nor from Swedish Match; 5-methylchrysene concentrations in STPs are only available from one publication (Stepanov et al. 2010). Swedish Match analyzed eight PAHs listed for their carcinogenic potential, including B[*a*]P and naphthalene.

In addition, several other PAHs that have not been categorized by IARC for their carcinogenic potential (either not evaluated or IARC Group 3) are frequently measured. Swedish Match analyzed eight "other PAHs".

Except for B[*a*]P and two of the "other" PAHs (fluoranthene and phenanthrene), concentrations of all PAHs analyzed were below their LOD (<30 ng/g dry weight) in all eight snus products (Table 4a). Further, the sum of all carcinogenic PAHs as well as the sum of all "other" PAHs were each below their combined LOD (<300 ng/g dry weight).

Table 4a: PAHs: Concentration in *General* Snus Brands (ng/g dry weight)

Analyte	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
	4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Carcinogenic PAHs								
B[*a*]P	<0.6	0.6	<0.6	0.60	<0.6	<0.6	1.2	0.8
PAH8* ¥	127.7	127.9	127.7	127.9	127.7	127.7	128.5	128.1
Sum of Carcinogenic PAHs	<300	<300	<300	<300	<300	<300	<300	<300
Other PAHs								
Fluoranthene	58	60.2	<30	74.4	<30	62.3	54.4	<30
Phenanthrene	<30	<30	<30	54.4	<30	<30	115.0	<30
Sum of Other PAHs	<300	<300	<300	<300	<300	<300	<300	<300

PS: pouched snus; WL: white large; OL: original large; OM: original mini. All concentrations in dry weight
¥ sums from concentrations <LOD, except for B[*a*]P
* PAH4 could not be calculated, since individual data for B[*b*]F was not available; PAH4: B[*a*]P, chrysene, B[*a*]A, B[*b*]F; PAH8: PAH4, B[*k*]F, B[*ghi*]P, DB[*ah*]A, I[*123cd*]P

Since B[*a*]P is well studied, it is often used as index chemical for the potency of other PAHs and as indicator for their presence. However, B[*a*]P may not always be present when other PAHs

may be detected. For example, in analyses of food samples, B[*a*]P was not detected in 30% of samples where other PAHs listed for their carcinogenic potential were detected (EFSA 2008). The Panel on Contaminants in the Food Chain of the European Food Safety Authority (EFSA) that evaluated the consequences of these findings for B[*a*]P as an indicator substance[14] focused on PAHs for which oral carcinogenicity data were available. The panel concluded that B[*a*]P "is not a suitable indicator for the occurrence of PAHs in food" and instead proposed that four (PAH4: B[*a*]P, benz[*a*]anthracene, benzo[*b*]fluoranthene, chrysene) or eight PAHs (PAH8: PAH4, benzo[*k*]fluoranthene, benzo[*ghi*]perylene, dibenz[*a,h*]anthracene, indeno[*1,2,3-cd*]pyrene) are the most suitable indicators (EFSA 2008). In the present analysis, then, these indicator sets of four or eight PAHs were calculated where data were available to give a better estimate of the occurrence of PAHs in snus and compare the results with data for estimated dietary intakes.

Intake Estimates from Snus Consumption

Table 4b summarizes the estimated PAH intakes (concentrations below LOD or LOQ were calculated as described under Section 3.1) assuming 100% extraction. No extraction data for the specific Swedish Match snus products were available. A study of a new product marketed as snus under unrestricted use conditions (mostly 10-30 minutes use time) reported approximately 30% extraction of B[*a*]P from the product (Caraway and Chen 2012). An adjustment for this assumed extraction rate is provided at the bottom of the table for B*[a*]P, PAH8, naphthalene, the sum of carcinogenic PAHs, and the sum of "other" PAHs, as well as fluoranthene and phenanthrene.

Carcinogenic PAHs

The estimated B[*a*]P and PAH8 intakes from consumption of 12 g pouched snus range from 0.002 to 0.004 µg/day and 0.70 to 0.75 µg/day, respectively, for all pouched brands, except *General Dry Mint PSOM.*

For *General Dry Mint PSOM*, B[*a*]P and PAH8 intakes from consumption of 12 g/day of the product are calculated to be 0.011 µg/day and 1.14 µg/day, respectively. When assuming consumption of 12 portions/day (0.33 g/portion) instead, the estimated daily intakes are 0.004 µg/day and 0.38 µg/day, respectively.

Consumption of 32 g of *General Loose Snus* results in estimated B[*a]*P and PAH8 intakes of 0.011 µg/day and 1.72 µg/day.

The estimated naphthalene consumption for all snus products is in the range of 0.117 µg/day (0.063 µg/day when assuming consumption of 12 portions/day (0.33 g/portion) *General Dry Mint PSOM)* to 0.285 µg/day (all values based on concentrations below LOD).

[14] The Panel was "asked by the European Commission to determine if benzo[*a*]pyrene was still a suitable "indicator" for both occurrence and carcinogenic effects for the 16 other most relevant PAHs in food and, if not, to recommend other suitable indicators or concepts." (EFSA. 2008 http://www.efsa.europa.eu/en/press/news/contam080804.htm, accessed in August 2013).

Table 4b: PAHs: Estimated Daily Intakes from Consumption of *General* Snus Brands

Analyte	Unit	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Carcinogenic PAHs									
B[*a*]P	µg/day	0.002¥	0.003	0.002¥	0.004	0.002¥	0.002¥	0.011	0.011
B[*a*]P	µg/kg/day	3.4×10^{-5}	4.8×10^{-5}	3.4×10^{-5}	5.0×10^{-5}	3.5×10^{-5}	3.4×10^{-5}	15×10^{-5}	15×10^{-5}
B[*a*]P MOE		2,034,780	1,451,078	2,092,285	1,394,581	1,988,535	2,052,134	459,835	455,729
PAH8*	µg/day	0.72¥	0.72	0.70¥	0.75	0.74¥	0.72¥	1.14	1.72
PAH8	µg/kg/day	0.010	0.010	0.010	0.011	0.011	0.010	0.016	0.025
PAH8 MOE		47,320	47,658	48,658	45,803	46,245	47,724	30,064	19,926
Additional Carcinogenic PAHs									
D[*a,h*]A	µg/day	0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
B[*a*]A		0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
B[*b,k*]F		0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
Chrysene		0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
I[*1,2,3-cd*]P		0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
Naphthalene		0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
Sum Carc. PAHs		1.20¥	1.19¥	1.17¥	1.24¥	1.23¥	1.19¥	1.88¥	2.85¥
Other PAHs									
Acenaphthene	µg/day	0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
Acenaphtylene		0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
Anthracene		0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
Benzo*[g,h,i]*perylene		0.120¥	0.119¥	0.117¥	0.124¥	0.123¥	0.119¥	0.188¥	0.285¥
Fluoranthene		0.329	0.339	0.117¥	0.436	0.123¥	0.351	0.483	0.285¥

Table 4b: PAHs: Estimated Daily Intakes from Consumption of *General* Snus Brands

Analyte	Unit	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Fluorene	µg/day	0.120[¥]	0.119[¥]	0.117[¥]	0.124[¥]	0.123[¥]	0.119[¥]	0.188[¥]	0.285[¥]
Phenanthrene		0.120[¥]	0.119[¥]	0.117[¥]	0.319	0.123[¥]	0.119[¥]	1.02	0.285[¥]
Pyrene		0.120[¥]	0.119[¥]	0.117[¥]	0.124[¥]	0.123[¥]	0.119[¥]	0.188[¥]	0.285[¥]
Sum other PAHs		1.20[¥]	1.19[¥]	1.17[¥]	1.24[¥]	1.23[¥]	1.19[¥]	1.88[¥]	2.85[¥]
Select PAHs *(assuming 30% extraction)*									
B[*a*]P	µg/day[#]	0.0007[¥]	0.0010[¥]	0.0007[¥]	0.0011	0.0007[¥]	0.0007[¥]	0.0032	0.0032
PAH8*		0.217[¥]	0.216[¥]	0.211[¥]	0.225	0.223[¥]	0.216[¥]	0.342	0.516
Naphthalene		0.036[¥]	0.036[¥]	0.035[¥]	0.037[¥]	0.037[¥]	0.036[¥]	0.057[¥]	0.086[¥]
Sum carc. PAH		0.361[¥]	0.358[¥]	0.351[¥]	0.373[¥]	0.370[¥]	0.358[¥]	0.565[¥]	0.855[¥]
Fluoranthene		0.099	0.102	0.035[¥]	0.131	0.037[¥]	0.105	0.145	0.086[¥]
Phenanthrene		0.036[¥]	0.036[¥]	0.035[¥]	0.096	0.037[¥]	0.036[¥]	0.306	0.086[¥]
Sum other PAH		0.361[¥]	0.358[¥]	0.351[¥]	0.373[¥]	0.370[¥]	0.358[¥]	0.565[¥]	0.855[¥]

PS: pouched snus; WL: white large; OL: original large; OM: original mini. All concentrations in dry weight
MOE: Margin of Exposure = BMDL10 (mg/kg/d)/daily intake from snus (mg/kg/d); for BMDL10 values used see footnote 16
[#] assuming 30% extraction
[¥] Intake estimates from concentrations <LOD
* PAH4 could not be calculated, since individual data for B[*b*]F was not available; PAH4: B[*a*]P, chrysene, B[*a*]A, B[*b*]F; PAH8: PAH4, B[*k*]F, B[*ghi*]P, DB[*ah*]A, I[*123cd*]P
Digits were rounded to the nearest thousandth decimal which may influence the re-generation of some of the values in the table.

Other PAHs

The estimated fluoranthene and phenanthrene intakes from consumption of 12 g pouched snus range from 0.117 to 0.351 µg/day and 0.117 to 0.319 µg/day, respectively, for all pouched brands, except *General Dry Mint PSOM.*

For *General Dry Mint PSOM,* fluoranthene and phenanthrene intakes from *General Dry Mint PSOM* consumption of 12 g/day are calculated to be 0.483 µg/day and 1.02 µg/day, respectively. When assuming consumption of 12 portions/day (0.33 g/portion) instead, the estimated daily intakes are 0.161 µg/day and 0.34 µg/day, respectively.

Consumption of 32 g of *General Loose Snus* results in estimated fluoranthene and phenanthrene intakes of 0.285 µg/day each (values based on concentrations below LOD).

PAHs - Worst Case

For the worst case scenario calculation, maximum concentrations in Swedish Match snus brands were only available for B[*a*]P (3 ng/g), the sum of carcinogenic PAHs (below LOD), the sum of other PAHs (510 ng/g), and PAH4 (<30 ng/g) from the 2011 Brand Testing data; all data per dry weight.

Using a 95th percentile consumption of 24 g/day pouched snus adjusted for the moisture of each individual product yields estimated maximum intake values up to 0.034, 5.97 and 0.25 µg/day for B[*a*]P, the sum of other PAHs, and PAH4, respectively, for all pouched snus products except *General Dry Mint PSOM.*

For *General Dry Mint PSOM, u*sing a 95th percentile consumption of 24 g/day adjusted for the moisture of *General Dry Mint PSOM* yields estimated maximum intake values of 0.05, 9.05, 0.38 µg/day for B[*a*]P, the sum of other PAHs, and PAH4, respectively. When consumption of 24 portions/day is assumed, the estimated maximum intakes were 0.02, 3.02, 0.13 µg/day, respectively.

Using a 95th percentile consumption of 77 g/day loose snus adjusted for the moisture of *General Loose Snus* yields estimated maximum intakes value of 0.097, 16.5 and 0.69 µg/day for B[*a*]P, the sum of other PAHs, and PAH4, respectively.

Comparison with Intake from Dietary Sources

Carcinogenic PAHs

The estimated daily intake of B*[a*]P from average snus consumption is on the lower end of or below the range of median dietary intakes across various countries (JECFA 2005), and even under worst case conditions is below the overall average (median) dietary exposure across European countries (EFSA 2008; see Table 4c).

For PAH8, the estimated intake from average consumption of pouched snus products is below intakes from the overall average (median) dietary exposure across European countries. Intake of PAH8 from consumption of *General Loose Snus* is within the range of intakes from dietary sources (EFSA 2008; see Table 4c).

The estimated PAH4 intake from snus products calculated using the worst case scenario conditions is below the range of overall average (median) dietary exposure across European countries (EFSA 2008; see Table 4c).

The estimated naphthalene intake from average consumption of snus products is well below the range from dietary intake (EPA 2003a; see Table 4c).

Based on the margin of exposure (MOE) approach[15], EFSA (2008) concluded that the MOEs calculated for B[*a*]P and PAH8 (17,949 and 17,014, respectively) indicate a low concern for consumer health at the average estimated dietary exposure. Similarly, based on the MOE approach, oral intake of these PAHs from snus consumption would be of low concern. Respective MOEs calculated for PAH intake from average snus consumption are in the ranges 455,729 to 2,092,285 and 19,926 to 48658 for B[*a*]P and PAH8, respectively. For worst case snus consumption, the MOEs for B[*a*]P and PAH4 are 144,118 and 95,200, respectively, for pouched snus, and 50,515 and 34,493, respectively, for loose snus. Therefore, these components are a low priority (MOE = 10,000-1,000,000) and very low priority (MOE >1,000,000) at the concentrations present in snus (Table 4b).

Other PAHs

The estimated fluoranthene and phenanthrene intakes from average consumption of all snus products are within the range of means of daily intake reported for European adults (SCF 2002; see Table 4c).

Published Risk Assessments for PAHs in Snus

Two assessments of cancer risk from exposure to B[*a*]P in STPs, including "Swedish snus"[16], were recently published (Ayo-Yusuf and Connolly 2011; Haussmann 2012).

Ayo-Yusuf and Connolly 2011

To calculate the cancer risk for B[*a*]P, Ayo-Yusuf and Connolly (2011) used the TD_{50} for tumors in the stomach developed in rats after chronic dietary administration of B[*a*]P as provided by the CPDB, and the amount of estimated B[*a*]P equivalents (eq) in the STPs. The B[*a*]P equivalents were derived using toxic equivalent factors (Ayo-Yusuf and Connolly 2011) and the assumption that other PAHs present in STPs double the B[*a*]P_{eq} (double the concentration of B[*a*]P) based on data by Stepanov et al. (2010), who analyzed PAHs in new products marketed as snus. Based on these assumptions, the cancer risk estimate for STPs meeting the GOTHIATEK® Standard limits was calculated to be 2.7 $x10^{-6}$ (with 100% transfer) and 1.6 $x10^{-7}$ (with 60% bioavailability). For "Swedish snus", with a median B[*a*]P_{eq} concentration of 3.68 ng/g dry weight and daily use of 10 g dry weight the reduced transfer cancer risk was calculated to be 9.0 $x10^{-8}$ (see also Section 4.3.3).

[15] MOE: Margin of Exposure = BMDL10 (mg/kg/d)/daily exposure (mg/kg/d); the MOE approach is based on the bench mark dose lower confidence limit for a 10% increase in the number of tumor bearing animals compared to control animals (BMDL10). The BMDL10 was calculated to be 0.07 mg/kg/d for B[a]P and 0.49 mg/kg/d for PAH8, respectively, based on total tumor-bearing animals in the 2-year oral carcinogenicity study of coal tar mixtures by Culp et al. (1998) (EFSA 2008).

[16] Data used was from analyses of *Du Maurier* snus, a new product marketed as snus, by Rickert and colleagues (2009)

Haussmann 2012

Haussmann (2012) calculated a theoretical ILCR for B[*a*]P, based on the oral cancer slope factor of 12 $(mg/kg/d)^{-1}$ established by CalEPA, for concentrations in STPs meeting the GOTHIATEK® Standard limit[17] and assuming 36% bioavailability. Therefore, his estimate is for an STP containing a concentration of 0.02 μg/g dry weight B[*a*]P The resulting theoretical ILCR was 5.3×10^{-6}. Based on his calculation of ILCRs for five other components, Haussmann attributed B[*a*]P a relative contribution of 0% to the total ILCR; that is, Haussmann concluded that exposure to B[*a*]P in snus products assumed to contain B[*a*]P at the GOTHIATEK® Standard limit did not contribute to excess cancer risk.

[17] GOTHIATEK® Standard limit for B[*a*]P given as the previous limit of 20 ng/g dry weight; this has since changed to 5 ng/g dry weight.

Table 4c: PAHs: Concentrations in Foods and Estimated Dietary Intakes

PAHs	IARC Group	Concentrations in Food	Estimated Daily Intake from Food and/or Beverages	Guideline Values and Health Basis#
Carcinogenic Polycyclic Aromatic Hydrocarbons				
Benzo[*a*]pyrene (B[*a*]P) *,	1	ND-212 μg/kg in meat, ND–173 μg/kg in fish, ND-1.5 μg/kg in fruits, ND-5.4 μg/kg in cereal, ND-164 μg/kg in oil, ND-0.60 μg/kg in beverages and ND-1.3 μg/kg in dairy products (JECFA 2005)	Mean intakes: 0.28 μg/d, range of means: 0.0014-0.42 μg/d (JECFA 2005) EU countries, median intake of mean dietary consumers: 235 ng/d, range of averages: 185-255 ng/d (EFSA 2008).	$BMDL_{10}$ of 0.07 mg/kg/d for B[a]P as a marker for the carcinogenic PAHs in food (EFSA 2008)
Naphthalene	2B	ND-156 μg/kg in meat, milk, fish, fruits, cereal, oil, and dairy products (JECFA 2005).	Average: 2.8-16.6 μg/d (EPA 2003a)	RfD: 0.02 mg/kg/day, based on a NOAEL of 100 mg/kg/d for the absence of decreased mean terminal body weight in male rats exposed by gavage for 13 weeks (ATSDR 2005).
PAH8	N/A	N/A	EU countries, median intake of mean dietary consumers: 1,729 ng/d (range of averages, 1,415-2,136 ng/d) (EFSA 2008).	$BMDL_{10}$ of 0.49 mg/kg/d for PAH8 as a marker for the carcinogenic PAHs in food (EFSA 2008)
PAH4	N/A	N/A	EU countries, median intake of mean dietary consumers: 1,168 ng/d (range of averages, 936-1,449 ng/d) (EFSA 2008).	$BMDL_{10}$ of 0.34 mg/kg/d for PAH4 as a marker for the carcinogenic PAHs in food (EFSA 2008)
Other Polycyclic Aromatic Hydrocarbons				
Fluoranthene	3	ND-376 μg/kg in meat, milk, fish, fruits, cereal, oil and dairy products (JECFA 2005).	EU, range of means for adults: <0.35-1.66 μg/d per person. (SCF 2002)	MRL (intermediate): 0.4 mg/kg/d, based on LOAEL of 125 mg/kg/d for increased relative liver weight in male mice (ATSDR 2005).
Phenanthrene	3	ND-618 μg/kg in meat, milk, fish, fruits, cereal, oil and dairy products (JECFA 2005).	EU, range of means for adults: <0.33-4.51 μg/d per person (SCF 2002)	No data

BMD: benchmark dose; BMDL: benchmark dose lower confidence limit; LOAEL: lowest observed adverse effect level; MRL: minimum risk levels; ND: non-detect; NOAEL: no observed adverse effect level; RfD: reference dose
*GOTHIATEK® Standard limits established.

4.4.3 Aldehydes

The current FDA HPHC list contains four aldehydes (FDA 2012). They are listed based on their carcinogenic potential (acetaldehyde, crotonaldehyde, formaldehyde), and potential toxicity to the cardiovascular system (acrolein), or to the respiratory system (acetaldehyde, acrolein, formaldehyde). Acetaldehyde is also listed for its potential to contribute to addiction.

Table 5a summarizes the aldehyde concentrations detected in the eight Swedish Match snus products. Only acetaldehyde and formaldehyde were present in detectable amounts in all products with one exception: in *General PSWL,* crotonaldehyde was detected at a concentration slightly above the LOD.

Table 5a: Aldehydes: Concentration in *General* Snus Brands (µg/g dry weight)

Analyte	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
	4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Acetaldehyde	26	23	30	28	33	25	10	24
Formaldehyde	9.3	10	12	9.9	8.7	9.3	6.1	7.3
Acrolein	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25
Crotonaldehyde	<0.25	<0.25	<0.25	<0.25	0.3	<0.25	<0.25	<0.25

PS: pouched snus; WL: white large; OL: original large; OM: original mini.

Intake Estimates from Snus Consumption

Table 5b summarizes the estimated aldehyde intakes (concentrations below LOD or LOQ were calculated as described under Section 3.1) assuming 100% extraction. No additional extraction data were available.

Table 5b: Aldehydes: Estimated Daily Intakes from Consumption of *General* Snus Brands (µg/d)

Analyte	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
	4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Acetaldehyde	148	129	166	164	192	141	88.8	323
Formaldehyde	52.8	56.3	66.2	58.0	50.5	52.3	54.2	98.1
Acrolein	1.00[¥]	0.99[¥]	0.98[¥]	1.04[¥]	1.03[¥]	0.99[¥]	1.57[¥]	2.38[¥]
Crotonaldehyde	1.00[¥]	0.99[¥]	0.98[¥]	1.04[¥]	1.74	0.99[¥]	1.57[¥]	2.38[¥]

PS: pouched snus; WL: white large; OL: original large; OM: original mini.
[¥] Intake estimates from concentrations <LOD

The estimated acetaldehyde and formaldehyde intakes from consumption of 12 g pouched snus range from 89 to 192 µg/day and 50.5 to 66.2 µg/day, respectively, for all pouched brands.

Consumption of 32 g of *General Loose Snus* results in estimated acetaldehyde and formaldehyde intakes of 323 µg/day and 98.1 µg/day, respectively.

The estimated acrolein and crotonaldehyde intakes (both calculated based on concentrations that were below their respective LOD for all but one product, where crotonaldehyde was quantified) were both in the range of 0.98 to 2.38 µg/day.

Aldehydes - Worst Case

For the worst case scenario calculation, maximum concentrations in Swedish Match snus brands from the 2011 Brand Testing data were only available for acetaldehyde (59.1 µg/g dry weight) and formaldehyde (33.6 µg/g dry weight).

Using a 95th percentile consumption of 24 g/day pouched snus adjusted for the moisture of each individual product yields estimated maximum intake values up to 692 and 394 µg/day for acetaldehyde and formaldehyde, respectively, for all pouched snus products except *General Dry Mint PSOM.*

For *General Dry Mint PSOM,* using a 95th percentile consumption of 24 g/day adjusted for moisture content yields estimated maximum intake values of 1,050 and 597 µg/day for acetaldehyde and formaldehyde, respectively. When consumption of 24 portions/day is assumed instead, the estimated maximum intakes are 350 and 199 µg/day, respectively.

Using a 95th percentile consumption of 77 g/day loose snus adjusted for the moisture of *General Loose Snus* yields estimated maximum intake values of 1,911 and 1,087 µg/day for acetaldehyde and formaldehyde, respectively.

Comparison with Intake from Dietary Sources

The estimated daily intakes of acetaldehyde and formaldehyde from average snus consumption are well below the average or the range of usual dietary intakes (ATSDR 1999a; EFSA 2010b; see Table 5c). Even under worst case conditions, the estimated daily intakes of these components from snus consumption are below the average or on the lower end of the range of estimated dietary intakes; the worst case intakes were more than three and ten times lower than the current TDI and RfD, respectively (EFSA 2010b; EPA 2012e; see Table 5c).

The estimated acrolein intake from average consumption of snus products (based on concentrations below LOD) is approximately 10 times lower than the RfD (EPA 2003b; see Table 5c). Dietary intake values have not been established for acrolein.

The estimated crotonaldehyde intake from average snus consumption is above the range of estimated usual daily dietary intake (WHO 2008; Table 5c). However, the estimated daily intake from snus is within the range of amounts that may be ingested from consumption of 100 to 200 g of certain fish or meats and lower than what may be ingested from alcoholic beverages such as wine (Eder and Budiawan 2001; WHO 2008; see Table 5c). It should be noted that these

estimates are based on calculated concentrations (that were below LOD) for all products except one. Crotonaldehyde was only detected in *General PSWL*.

In agreement with this, Stepanov and colleagues (2008) concluded that the overall levels of aldehydes in the STPs analyzed in their study were relatively low compared to other sources of exposure such as diet and alcoholic beverages. In that study, concentrations of acetaldehyde and formaldehyde in *General* snus were very similar to the concentrations in the Swedish Match analysis of the eight snus products analyzed in the present study, but acrolein and crotonaldehyde concentrations detected were three times higher than the current Swedish Match LOD (Stepanov et al. 2008).

Table 5c: Aldehydes: Concentrations in Foods and Estimated Dietary Intakes

Aldehydes	IARC Group	Concentrations in Food	Estimated Daily Intake from Food and/or Beverages	Guideline Values and Health Basis#
Acetaldehyde	2B	Fruits and juices (0.3–50 mg/kg); peas (1.2-400 mg/kg); other vegetables (up to 22 mg/kg), Bread (4.2–9.96 mg/kg), cereals (up to 3.5 mg/kg), Yoghurt (0.7-76 mg/kg), other milk products (up to 8 mg/kg), Wine (white) (7.3-142 mg/kg) (EFSA 2010b).	US intakes: 9,700 µg/d EU intakes: 11,000 µg/d (EFSA 2010b).	TDI: 0.1 mg/kg/d** (EFSA 2010b). Based on toxicity profiles similar to methaldehyde. A 2-year oral rat study and a 3-generation oral rat study including teratogenicity with methaldehyde. (SCF 1998 as cited in EFSA 2010b)
Formaldehyde	1	≤ 60 mg/kg in some fruits and marine fish based on Health Canada data (ATSDR 2010).	Range: 1,000–10,000 µg/d (ATSDR 1999a).	RfD: 0.2 mg/kg/d, based on gastrointestinal damage (EPA 2012e, last revised 1990) MRL (chronic): 0.2 mg/kg/d, based on a NOAEL of 15 mg/kg/day for lack of gastrointestinal effects in male rats (ATSDR 1999a; ATSDR 2010).
Acrolein	3	0.01-0.05 mg/kg in vegetables 290-1300 ppb in cheese (IARC 1995) <40 µg/g in food products raw cocoa beans, volatiles from cooked mackerel and white bread, and vegetable oils and in most instances <1 µg/g (ATSDR 2007a).	Not quantified (ATSDR 2007a).	RfD: 0.0005 mg/kg/d, based on a NOAEL of 0.05 mg/kg/day for decreased survival in male and female rats treated by oral gavage for 2 years (EPA 2003b). MRL (Intermediate): 0.004 mg/kg/d, based on gastrointestinal effects (ATSDR 2007a).
Crotonaldehyde	3	<0.01- 0.7 mg/kg (<0.01-0.7 µg/g) vegetables, bread, cheese, milk, meat, fish (IARC 1995) Fruits and vegetables: 1.4-100 µg/kg. Fish: 71.4-100 µg/kg and Meat: 10-270 µg/kg (WHO 2008); alcoholic beverages, e.g., wine: 300-1,240 µg/L (Eder and Budiawan 2001).	Range: 0.01-0.83 µg/d (WHO 2008)	No data

MRL: minimum risk levels; NOAEL: no observed adverse effect level; RfD: reference dose; TDI: tolerable daily intake
* GOTHIATEK® Standard limits established;
**Based on manufacture of plastic materials and articles intended to come into contact with foodstuffs and derived for acetaldehyde and vinyl propionate.

4.4.4 Metals/Metalloids

Metals and metalloids on the FDA HPHC list are arsenic, beryllium, cadmium, chromium, cobalt, lead, mercury, nickel, and selenium. Both the elemental form of the metals and metal-bound compounds are referred to in this list. In addition to their carcinogenic potential, arsenic, cobalt, and lead are considered potential cardiovascular toxicants (FDA 2012). The HPHC list classifies selenium based on its potential effects on the respiratory system; cadmium, chromium, and nickel are also listed as respiratory toxicants. Arsenic, cadmium, chromium, lead, and mercury are listed as potential reproductive and developmental toxicants (FDA 2012).

Table 6a summarizes the average metal/metalloid concentrations detected in the eight Swedish Match snus products. Beryllium and mercury were not detectable in any of the snus products; arsenic was detected in two products: *General Classic Blend PSWL* and *General PSOL*. No data for cobalt was available.

Table 6a: Metals/Metalloids: Concentration in *General* Brands (µg/g dry weight)

Analyte	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
	4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Arsenic	<0.10	<0.10	0.21	0.19	<0.10	<0.10	<0.10	<0.10
Beryllium	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Cadmium	0.350	0.410	0.39	0.37	0.45	0.45	0.400	0.460
Chromium	0.60	0.48	1.00	0.84	0.54	0.55	0.85	0.58
Lead¤	0.210	0.200	0.350	0.350	0.230	0.250	0.240	0.230
Mercury	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
Nickel¤	1.30	1.10	1.00	1.00	0.87	1.00	1.30	1.30
Selenium	0.10	<0.05	<0.05	0.18	0.14	0.13	0.11	0.14

PS: pouched snus; WL: white large; OL: original large; OM: original mini.

Intake Estimates from Snus Consumption

Table 6b summarizes the estimated metal/metalloid intakes (concentrations below LOD or LOQ were calculated as described under Section 3.1) assuming 100% extraction. Some information was available for extraction of cadmium (3-11%) and lead (negligible) from Swedish snus. A study with a new product marketed as snus indicates that both cadmium and nickel were extracted at approximately 10%; a study on moist snuff products indicates that metals in general are extracted at rates of less than 65%, beryllium at 10% and lead less than 10% (see ENVIRON Snus Monograph 2013, Section 2.3.6.4).

Table 6b: Metals/Metalloids: Estimated Daily Intakes from Consumption of *General* Snus Brands (µg/day)

Analyte	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
	4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Assuming 100% extraction								
Arsenic	0.40¥	0.40¥	1.16	1.11	0.41¥	0.40¥	0.63¥	0.95¥
Beryllium	0.20¥	0.20¥	0.20¥	0.21¥	0.21¥	0.20¥	0.31¥	0.48¥
Cadmium	1.99	2.31	2.15	2.17	2.61	2.53	3.55	6.18
Chromium	3.41	2.70	5.52	4.92	3.14	3.10	7.55	7.80
Lead¤	1.19	1.13	1.93	2.05	1.34	1.41	2.13	3.09
Mercury	0.08¥	0.08¥	0.08¥	0.08¥	0.08¥	0.08¥	0.13¥	0.19¥
Nickel¤	7.38	6.19	5.52	5.86	5.05	5.63	11.5	17.5
Selenium	0.57	0.20¥	0.20¥	1.05	0.81	0.73	0.98	1.88
Assuming 10% extraction								
Beryllium	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.05
Cadmium	0.20	0.23	0.22	0.22	0.26	0.25	0.36	0.62
Lead	0.12	0.11	0.19	0.20	0.13	0.14	0.21	0.31
Nickel	0.74	0.62	0.55	0.59	0.51	0.56	1.15	1.75

PS: pouched snus; WL: white large; OL: original large; OM: original mini.
¥ Intake estimates from concentrations <LOD

The estimated metal/metalloid intakes from consumption of 12 g pouched snus, except *General Dry Mint PSOM,* are as follows*:*

When conservatively 100% extraction is assumed -

- 0.4 to 1.2 µg/day arsenic
- 0.2 µg/day beryllium (based on concentrations below LOD)
- 2.0 to 2.6 µg/day for cadmium
- 2.7 to 5.5 µg/day for chromium
- 1.1 to 2.1 µg/day for lead
- 0.08 µg/day mercury (based on concentrations below LOD)
- 5.1 to 7.4 µg/day for nickel
- 0.2 to 1.1 µg/day selenium

Where some extraction data indicated extraction might be approximately 10% or less - 0.02 µg/day beryllium, 0.2 to 0.3 µg/day for cadmium, 0.1 to 0.2 µg/day for lead, 0.5 to 0.7 µg/day for nickel.

Intakes from *General Dry Mint PSOM* consumption of 12 g/day are presented in Table 6b, above. When assuming consumption of 12 portions/day (0.33 g/portion) instead, the estimated daily intakes are as follows:

When conservatively 100% extraction is assumed -

- 0.2 µg/day for arsenic (based on concentrations below LOD)
- 0.1 µg/day beryllium (based on concentrations below LOD)
- 1.2 µg/day cadmium
- 2.5 µg/day for chromium
- 0.7 µg/day for lead
- 0.04 µg/day for mercury (based on concentrations below LOD)
- 3.8 µg/day for nickel
- 0.3 µg/day for selenium

Where some extraction data indicated extraction might be approximately 10% or less - 0.01 µg/day for beryllium, 0.12 µg/day for cadmium, 0.07 µg/day lead, and 0.38 µg/day for nickel.

For *General Loose Snus,* based on consumption of 32 g/day the estimated daily intakes are as follows:

When conservatively 100% extraction is assumed -

- 1.0 µg/day for arsenic (based on concentrations <LOD)
- 0.5 µg/day beryllium (based on concentrations <LOD)
- 6.2 µg/day cadmium
- 7.8 µg/day for chromium
- 3.1 µg/day for lead
- 0.2 µg/day for mercury (based on concentrations <LOD)
- 18 µg/day for nickel
- 1.9 µg/day for selenium

Where some extraction data indicated extraction might be approximately 10% or less - 0.05 µg/day for beryllium, 0.6 µg/day for cadmium, 0.3 µg/day lead, and 1.8 µg/day for nickel.

Metals/Metalloids - Worst Case

For the worst case scenario calculation, maximum concentrations in Swedish Match snus brands from the 2011 Brand Testing data were only available for arsenic (0.25 µg/g), cadmium (1.1 µg/g), chromium (1.7 µg/g), lead (0.46 µg/g), and nickel (3.9 µg/g); all concentrations per dry weight.

Using a 95th percentile consumption of 24 g/day pouched snus adjusted for the moisture of each individual product yields estimated maximum intake values up to 2.9 µg/day arsenic, 13 µg/day cadmium, 20 µg/day chromium, 5.4 µg/day lead, and 46 µg/day nickel, for all pouched snus products except *General Dry Mint PSOM.*

For *General Dry Mint PSOM,* using a 95th percentile consumption of 24 g/day adjusted for moisture yields estimated maximum intake values of 4.4 µg/day arsenic, 20 µg/day cadmium, 30 µg/day chromium, 8.2 µg/day lead, and 69 µg/day nickel. When consumption of 24

portions/day is assumed instead, the estimated maximum intake values are 1.5 µg/day arsenic, 6.5 µg/day cadmium, 10 µg/day chromium, 2.7 µg/day lead, and 23 µg/day nickel.

For *General Loose Snus,* using a 95th percentile consumption of 77 g/day loose snus adjusted for moisture yields estimated maximum intake values of 8.1 µg/day arsenic, 36 µg/day cadmium, 55 µg/day chromium, 15 µg/day lead, and 126 µg/day nickel.

Comparison with Intake from Dietary Sources

Arsenic

The estimated daily intake of arsenic from average snus consumption is below the range of dietary intake in the US, even under worst case conditions of pouched snus consumption; under worst case conditions of *General Loose Snus* consumption it is within the range of dietary intakes, and more than half of the current RfD (EPA 2012a; JECFA 2010a; see Table 6c).

Beryllium

The estimated daily intake of beryllium from average snus consumption calculated from concentrations below the LOD and assuming 100% extraction is higher than the estimated average dietary intake from US food (based on an beryllium content in 0.1 ng/g food for total diet), but below the range reported in some other studies Table 6c). However, the extraction rate of beryllium from STPs is much lower (see above). Adjusting for a 10%-extraction rate from snus, results in intake values that are below the estimated average intake from diet.

Cadmium

The estimated daily intake of cadmium from average snus consumption and assuming 100% extraction is below the geometric mean dietary intake in the US (IARC 2012c; see Table 6c), and even under worst case conditions of pouched snus consumption. Under worst case conditions of *General Loose Snus* consumption, the estimated daily intake of cadmium assuming 100% extraction is below the current RfD for food and at the RfD for drinking water; adjusted to an extraction rate of 10 to 50%, it is below or at the geometric mean dietary intake in the US (EPA 2012b; JECFA 2010b; see Table 6c). It should also be noted that cadmium absorption from the gastrointestinal tract is low (5-10% (ATSDR 2012a)). Available biomarker data for cadmium in snus users confirms that exposure to this metal is not different from non-users of tobacco (see ENVIRON Snus Monograph (2013), Section 3.2.4.1).

Chromium

The estimated daily intake of chromium (unspecified element species) is, even under worst case conditions of pouched snus consumption and assuming 100% extraction, below the range of US mean dietary chromium intake; under worst case conditions of *General Loose Snus* consumption, chromium intake from snus use is within the range of dietary intake and below the current RfD established for Cr VI exposure from drinking water (ATSDR 2012b; see Table 6c; EPA 2012d).

Lead

The estimated daily intake of lead from average consumption of snus products assuming 100% extraction is similar to US mean dietary intake estimates (JECFA 2010b; see Table 6c).

However, considering the very low extraction rate of lead (<10%) from snus products, this is likely a strong overestimation. Accounting for an extraction rate of approximately 10%, the lead intake from average snus consumption is well below the dietary intake estimates reported for the US population. Under worst case conditions without accounting for extraction, the lead intake from snus consumption is less than half of both the $BMDL_{01}$ and $BMDL_{10}$ established by EFSA (2010a) for cardiovascular effects and kidney effects, respectively (see Table 6c). However, since extraction is likely much lower than 100% and closer to 10% or less, even under worst case conditions of snus consumption, lead intake is similar to the mean dietary intake.

Mercury

The estimated daily intake of mercury from average snus consumption (calculated from concentrations below LOD) is below the range of average dietary intakes reported for the US (JECFA 2010a; see Table 6c).

Nickel

The estimated daily intake of nickel from average snus consumption and even from worst-case pouched snus consumption is, with and without taking extraction rates into account, well below the range of dietary intakes reported for the US adult population; under worst case conditions of *General Loose Snus* consumption, the nickel intake from snus consumption assuming 100% extraction is within the range of usual dietary intakes (IARC 2011; see Table 6c).

Selenium

The estimated daily intake of selenium from average snus consumption is well below the range of dietary intakes reported for the US population (ATSDR 2003; see Table 6c). Available biomarker data for selenium in snus users confirms that exposure to this metalloid is not different from non-tobacco using controls (see ENVIRON Snus Monograph (2013), Section 3.2.4.2).

Published Risk Assessments for Select Metals in Snus

Ayo-Yusuf and Connolly 2011

In the study by Ayo-Yusuf and Connolly (2011), see also Sections 4.3.3 and 4.4.2 that used GOTHIATEK® levels for several components in STPs to evaluate implications for product regulations, the authors came to a different conclusion with respect to cadmium than the present analysis. They stated that "if a 70 kg adult uses 10 g dry weight equivalent of STPs containing 1000 ng/g of cadmium [1 μg/g], this will result in an exposure equivalent to 0.0006 mg/kg body weight/day, which is higher than the reference dose (0.0005 mg/kg) specified for chronic oral ingestion that may result in significant proteinuria." It is, however, unclear how these authors arrived at their conclusion: The intake of 10 g/day 1 μg/g cadmium would result in an intake of 10 μg/d or 0.143 μg/kg/day (0.00014 mg/kg/day) cadmium, lower than the drinking water RfD used by Ayo-Yusuf and Connolly (2011). These authors adjusted the average daily intake to life time average daily exposure by multiplying with 30 years of daily snuffing divided by 70 years of average lifetime, resulting in 0.00006 mg/kg/d cadmium intake, 8 times lower than the drinking water RfD of 0.0005 mg/kg/d and 10 times lower than the number given by

Ayo-Yusuf and Connolly (2011), indicating that there might be an error in decimal point. In addition, a 100% extraction rate appears to have been assumed for their calculation.

Ayo-Yusuf et al. (2011) also estimated a relative cancer risk for cadmium and lead based on the GOTHIATEK® Standard Limit as well as concentrations detected by Rickert and colleagues (2009) in "Swedish snus", using the $1/TD_{50}$ from animal studies reported by the CPDB as cancer potency factor without adjustments[b] Based on their calculations, the cancer risk from cadmium in STPs with 1 µg/g dry weight cadmium after adjustment for reduced oral absorption (6%) was 1.7 $x10^{-4}$ (0.00006 mg/kg/day x 1/0.0217 mg/kg/day x 0.06), 31 times less than that calculated for TSNAs. Note that the error was not repeated for this calculation. The cancer risk for lead in STPs with 2 µg/g dry weight lead was calculated to be 1.5 $x10^{-7}$ (0.000123 mg/kg/day x 1/46.6 mg/kg/day x 0.06), while for "Swedish snus" with 0.238 µg/g dry weight lead it was calculated to be 1.8 $x10^{-8}$.

Haussmann 2012

An equivalent analysis was conducted by Haussmann (2012), who used (oral) cancer slope factors from CalEPA[b] and the GOTHIATEK® Limit concentrations to estimate theoretical ILCRs from arsenic, cadmium, chromium and lead (1.7 $x10^{-5}$, 5.5 $x10^{-5}$, 2.8 $x10^{-5}$, 6.2 $x10^{-8}$, respectively). This author used 6% bioavailability for cadmium and lead, and 36% for arsenic and chromium. Based on these assumptions, he estimated that the relative contribution to the theoretical ILCRs from cadmium and chromium (assuming Cr VI) was each 1% – compared to 98% from NNK and NNN together, with negligible contributions of arsenic and lead.

Note that both Ayo-Yusuf and Connolly (2011) and Haussmann (2012) derived a cancer risk for cadmium based on data for inhalation exposure. The application to an oral exposure from snus consumption is clearly questionable. Human occupational exposure to cadmium occurs likely primarily via the inhalational route and oral studies in animals have not caused lung cancer (IARC 2012c).

[18] The TD_{50} for cadmium (0.0217 mg/kg/day) was derived for lung tumors in rats caused by inhalation exposure to cadmium sulfate aerosol; the TD_{50} for lead (46.6 mg/kg/day) was derived for kidney tumors in rats caused by lead acetate.

[19] Both the oral slope factor for arsenic (1.5 $x10^{0}$ $(mg/kg/day)^{-1}$) and cadmium (1.5 $x10^{1}$ $(mg/kg/day)^{-1}$) were derived from human occupational exposure lung cancer data; the oral slope factor for hexavalent chromium (Cr VI; 4.2 $x10^{-1}$ $(mg/kg/day)^{-1}$) was derived from female mouse benign and malignant stomach tumor data; the oral slope factor for lead (8.5 $x10^{-3}$ $(mg/kg/day)^{-1}$) was derived from rat kidney tumor incidence data (OEHHA 2011. Appendix B). Chemical specific summaries of the information used to derive unit risk and cancer potency values. (www.oehha.ca.gov/air/hot_spots/2009/AppendixB.pdf).

Table 6c: Metals/Metalloids: Concentrations in Foods and Estimated Dietary Intakes

Elements	IARC Group	Concentrations in Food	Estimated Daily Intake from Diet	Guideline Values and Health Basis[#]
Arsenic (As)*	1 (inorganic As)	2.4–16.7 mg/kg in marine fish, 3.5 mg/kg in mussels, and > 100 mg/kg in certain crustaceans), followed by meats, cereals, vegetables, fruit, and dairy products (ATSDR 2007b).	Inorganic As: US and various countries, range of means for: 6-180 μg/d** US, range of means: 4.8-12 μg/d** (JECFA 2010a)	Inorganic As: RfD: 0.0003 mg/kg/d, based on hyperpigmentation, keratosis and possible vascular complications (EPA 2012a, last revised 1993) MRL (chronic) : 0.0003 mg/kg/d based on hyperkeratosis and hyperpigmentation (ATSDR 2007b) $BMDL_{0.5}$: 3-5 μg/kg/d (JECFA 2010a) $BMDL_{01}$: 0.3-8 μg/kg/d (EFSA 2009b) both based on lung cancer $BMDL_{0.5}$: 5.2-11.4 μg/kg/d for urinary tract cancer (JECFA 2010a).
Beryllium (Be)	1	<0.1–2200 ug/kg, fresh weight. Highest in kidney beans, crisp bread, garden peas, parsley and pears (IARC 2012b).	US: 0.12 μg/d, based on an arbitrary value for Be content in total diet of 0.1 ng/g food (US EPA 1987 as cited in ATSDR 2002). Data reported in other studies were in the range of 5-100 μg/d (ATSDR 2002).	RfD: 0.002 mg/kg/d, based on a BMD of 0.46 mg/kg/d (EPA 2012a, last revised 1998) MRL (chronic): 0.002 mg/kg/d (ATSDR 2002) Both based on ulcerative lesions in dogs
Cadmium (Cd)*	1	<0.02 μg/g, higher in leafy vegetables, starchy roots, cereals and grains, nuts and pulses, medium in meat and fish	US geometric mean: 18.9 μg/d (IARC 2012c)	RfD: Food - 0.001 mg/kg/d; drinking water - 0.0005 mg/kg/d (EPA 2012d, last revised 1994); MRL (chronic) : 0.1 μg/kg/d (ATSDR 2012a); PTMI: 25 μg/kg per month (JECFA 2010b); TWI: 2.5 μg/kg per week (EFSA 2009a); All based on kidney dysfunction
Chromium (Cr)*	1 (Cr VI) 3 (Cr III)	<10-1300 μg/kg, highest concentrations in meat, fish, fruits, and vegetables water (ATSDR 2012b)	US mean chromium (unspecified): 35 μg/d, range: 21-61 μg/d (ATSDR 2012b)	*Cr VI (Drinking water exposure)* RfD: 0.003 mg/kg/d, based on a NOAEL for systemic effects in rats exposed to 2.5 mg/kg/d (EPA 2012d, last revised 1998). MRL (chronic): 0.001 mg/kg/d $BMDL_{10}$: 0.09 mg/kg/d (ATSDR 2012b) *Cr III* RfD: 1.5 mg/kg/d (EPA 2012c, last revised 1998). No MRLs for Cr (III)
Lead	2A	0.003 mg/kg	US range of means:	$BMDL_{01}$:1.50 μg/kg/d[$], based on

Table 6c: Metals/Metalloids: Concentrations in Foods and Estimated Dietary Intakes

Elements	IARC Group	Concentrations in Food	Estimated Daily Intake from Diet	Guideline Values and Health Basis#
(Pb)*^		(0.003 µg/g) - overall mean in foods such as pickles, beef liver, and canned foods (EFSA 2010a)	1.2-18 µg/d** (JECFA 2010b) US mean: 10.9 µg/d (ATSDR 2007c)	cardiovascular effects $BMDL_{10}$: 0.63 µg/kg/d$ based on kidney effects (EFSA 2010a)
Mercury (Hg)*	2B	Total Hg: 0.0001-0.050 mg/kg, in foods other than fish. 0.001-11.4 mg/kg in fish samples (JECFA 2010a)	Total Hg US range of averages, total diet: 0.6-1.2 µg/d** (JECFA 2010a)	PTWI (inorganic mercury): 4 µg/kg/week, based on $BMDL_{10}$ for kidney weight increase in male rats (JECFA 2010a) MRL (intermediate, inorganic Hg): 0.002 mg/kg/d based on renal effects MRL (chronic) methyl Hg: 0.003 mg/kg/d (21 µg/d) Based on neurodevelopmental outcomes in *in utero* exposures (ATSDR 1999b)
Nickel (Ni)*	1	0.01-0.1 mg/kg, as high as 8-12 mg/kg in cocoa beans, soybeans, nuts and grains (IARC 2011).	US adult population, range: 101–162 µg/d (IARC 2011)	RfD: 0.02 mg/kg/d (soluble salts), based on a NOAEL of 5 mg/kg/day and a LOAEL of 50 mg/kg/d for decreased body weight and organ weight in rats exposed to dietary nickel for 2 years (EPA 2012f, last revised 1996)
Selenium (Se)	3	0.07-0.65 mg/kg, milk, meat products, fruits and vegetables (ATSDR 2003).	US population median: 111 µg/d, , range: 71-152 µg/d (ATSDR 2003)	MRL (chronic): 0.005 mg/kg/d, based on a NOAEL of 0.015 mg/kg/d for disappearance of symptoms of selenosis in recovering individuals (ATSDR 2003)

BMDL: benchmark dose levels; LOAEL: lowest observed adverse effect level; MRL: minimum risk levels; NOAEL: no observed adverse exposure level; PTWI: provisional tolerable weekly intake; PTMI: provisional tolerable monthly intake; RfD: reference dose
* GOTHIATEK® Standard limits established;
^ JECFA data from TDS samples in the 2003 – 2006 NHANES. ATSDR data from EPA Region V
$ BMDL derived from studies on blood and bone lead levels; ** Based on a body weight of 60 kg, the standard value used for adults in the EU

4.4.5 Radioisotopes

The current HPHC list of the FDA contains polonium-210 (Po-210), uranium-238 (U-238), and uranium-235 (U-235) based on concerns about their carcinogenic potential (FDA 2012). FDA lists the latter two also for their potential to be respiratory toxicants.

Table 7a summarizes the polonium-210 activity detected in the eight snus products. Both uranium radioisotopes were not detected in any of the products (<1 Bq/kg as is). For U-238, activities were calculated as described in Section 3.1 (0.00071 Bq/g as is). In natural uranium, U-235 is 0.72% of total uranium or 0.73% of U-238 (NCRP 2009). Corrected for the relative specific activities of these radioisotopes, the U-235 activity level is approximately 5% of the U-238 activity level (0.00071 Bq/g as is × 0.05 = 0.000035 Bq/g as is).

Table 7a: Radioisotopes: Polonium-210 Activity in *General* Snus Brands and Estimated Intakes of Po-210, U-235, and U-238 from Consumption of *General* Snus Brands

Analyte	Unit	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Activity									
Po-210	Bq/g as is	0.003	<0.002	<0.002	0.006	0.007	0.002	0.006	0.004
Daily intake									
Po-210	Bq/d	0.04	0.02[¥]	0.02[¥]	0.07	0.08	0.02	0.07	0.13
U-238		0.0085[¥]	0.0085[¥]	0.0085[¥]	0.0085[¥]	0.0085[¥]	0.0085[¥]	0.0085[¥]	0.0226[¥]
U-235		0.00042*	0.00042*	0.00042*	0.00042*	0.00042*	0.00042*	0.00042*	0.00112*

PS: pouched snus; WL: white large; OL: original large; OM: original mini. As is = wet weight basis
[¥] Intake estimates from concentrations <LOD
*As 5% of U-238

Intake Estimates from Snus Consumption

Table 7a summarizes the estimated Po-210, U-238, and U-235 intakes (activities below LOD were calculated as described in Section 3.1) assuming 100% extraction. No other extraction information was available.

The estimated intake from consumption of 12 g snus is in the range of 0.02 and 0.08 Bq/day Po-210 for all pouched brands; uranium isotope intakes (calculated based on concentrations below LOD as described above) are 0.0085 Bq/day U-238 and 0.00042 Bq/day U-235.

Consumption of 32 g of *General Loose Snus* results in an estimated Po-210 intake of 0.13 Bq/day and intakes of 0.0226 Bq/day U-238 and 0.00112 Bq/day U-235.

Radioisotopes – Worst Case

Maximum activities of Po-210 (0.0085 Bq/g), U-238 (0.0015 Bq/g), and U-235 (<0.001 Bq/g) in Swedish Match snus brands were available from the 2011 Brand Testing data; all activities "as is".

Using a 95th percentile consumption of 24 g/day snus yields estimated maximum intake values of 0.204 Bq/day Po-210, 0.036 Bq/day U-238, and 0.0018 Bq/day U-235 (calculated based on a concentration < LOD and assuming 5% of U-238) for all pouched snus products.

Using a 95th percentile consumption of 77 g/day *General Loose Snus* yields estimated maximum intake values of 0.655 Bq/day Po-210, 0.116 Bq/day U-238, and 0.0058 Bq/day U-235 (calculated based on a concentration < LOD and assuming 5% of U-238).

Comparison with Intake from Dietary Sources

The estimated daily intake of Po-210 from average pouched snus consumption is similar to the reported average intake from the diet in the US (UNSCEAR 2000 as cited in HSDB 2006; see Table 7c). Average *General Loose Snus* consumption assuming use of 32 g product per day, is approximately two times the average dietary intake in the US, but is still in the range reported for other countries. Under worst case conditions the estimated daily intake of Po-210 from snus consumption is on the upper end of what has been reported for dietary intakes in various countries (UNSCEAR 2000 as cited in HSDB 2006; see Table 7c; Watson 1983). In particular, fish products and seafood are a source of this radioisotope.

A total daily uranium intake estimate from the diet was available. Because total uranium contains U-238 (low radioactivity), U-235, and U-234, and no experimental activity level for the latter was available, it was assumed that U-234 was in secular equilibrium with U-238 to calculate total uranium activity levels. Summing the activity levels for all three uranium isotopes (2x act (U-238) + act (U-235); ORISE[20]) accordingly, results in an estimated total uranium activity level of 0.00146 Bq/g. The estimated daily intakes calculated based on these assumptions are presented in Table 7b.

Average pouched and loose snus use results in a uranium intake that is in or close to the range of uranium intake estimated from the diet assuming a conservative extraction rate of 100%. However, the extraction rate of uranium from tobacco products is probably much lower than 100%, with uranium content likely mostly originating from the aerial deposition of relatively insoluble uranium from phosphate fertilizer on tobacco leaves (ATSDR 2013; Zielinski et al. 1997). It should also be noted that the calculation of average uranium intake from snus consumption is based solely on activity measures below the LOD, and that actual uranium concentrations in snus may be much lower than the values assumed here. Under worst case conditions with a conservative 100% extraction rate, the estimated uranium intake from pouched snus products and *General Loose Snus* is approximately two and ten times of the intake from diet, respectively. This estimate is approximately four times lower than both the TDIs by EFSA and UK Food Standards Agency (UK FSA) based on kidney toxicity, more than 20 times lower

[20] ORISE. Radiological and chemical properties of uranium. www.pbadupws.nrc.gov/docs/ML1122/ML11227A233.pdf, accessed September 2013.

than the current RfD for soluble uranium compounds, and almost 40 times lower than the TDI for insoluble uranium compounds established by the UK FSA, both also based on kidney toxicity (EFSA 2009c; EPA 2012g; UK FSA 2004; see Table 7c).

Table 7b: Uranium Daily Intake Estimates (Bq/day)

Analyte	Snus Consumption				Diet (ATSDR 2013)
	Average Pouched	Average *General Loose Snus*	Worst Case Pouched	Worst Case *General Loose Snus*	
U-238	0.0085	0.0226	0.036	0.116	0.011-0.0185
U-235	0.00042	0.00112	0.0018	0.0058	No data
Total Uranium*	0.0174 (0.7 µg/day)	0.0463 (1.8 µg/day)	0.0738 (2.9 µg/day)	0.238 (9.3 µg/day)	0.022-0.037 (0.9-1.5 µg/d)

1 pCi = 0.037 Bq; 1 µg = 0.69 pCi
* Total Uranium activity estimated based on act U-238 x 2 + act U-235

Table 7c: Radioactive Isotopes: Concentrations/Activities in Foods and Estimated Dietary Intakes

Radio-nuclides	IARC Group	Concentrations/ Activities in Food	Estimated Daily Intake from Diet	Guideline Values and Health Basis#
Po-210	1*	Highest concentrations reported in fish products 50-120,000 mBq/kg (UNSCEAR 2000 as cited in HSDB 2006).	US annual intake: 22 Bq/year (0.06 Bq/day), Argentina & Japan, range of annual intakes: 18-220 Bq/year (0.05-0.6 Bq/day) (UNSCEAR 2000 as cited in HSDB 2006) UK data range of intake: 1-10 pCi/d (0.037-0.37 Bq/d (Watson 1983).	No data
U-238	1*	No data	US range of intakes: 0.3-0.5 pCi/d (ATSDR 2013) UK total dietary exposure: 0.028 µg/kg/d (UK FSA 2004).	No data
U-235	1*	No data	No data	No data
Total U	1*	0.04-60 ng/g, raw weight in tea, vegetables, potatoes, breads, onions and meats (ATSDR 2013).	US range of intakes: 0.6-1.0 pCi/d (0.9–1.5 µg/d), based on consumption rates of root crops such as potatoes, parsnips, turnips, and sweet potatoes (EPA 1985c as cited in ATSDR 2013) Overall EU dietary exposure range: 3-5.4 µg/d (EFSA 2009c).	RfD for uranium soluble salts: 0.003 mg/kg/d, based on a LOAEL of 2.8 mg/kg/day for initial weight loss and moderate nephrotoxicity in rabbits exposed to uranium in the diet for 30 days (EPA 2012g, last revised 1989) TDI for insoluble uranium compounds: 5 µg/kg/d; TDI for soluble uranium compounds: 0.5 µg/kg/d (UK FSA 2004) 0.6 µg/kg/d based on LOAEL (0.06 mg/kg/day) for nephrotoxicity from 91-day study in male rats (EFSA 2009c). All based on kidney toxicity.

LOAEL: lowest observed adverse effect level; RfD: reference dose; TDI: total dietary intake
* Radionuclides. 1 pCi = 0.037 Bq

4.4.6 Other Trace-Level Components

The current HPHC list of the FDA contains acrylamide, aflatoxin B_1 and ethyl carbamate (urethane) based on concerns about their carcinogenic potential (FDA 2012). FDA lists the latter also for its potential for reproductive and developmental toxicity.

Table 8a summarizes the acrylamide concentration detected in the eight products. Ethyl carbamate and aflatoxin B_1 were not detected and the concentration of the sum of four aflatoxins (including aflatoxin B_1) was below the LOD in all eight snus products.

Table 8a: Other Components: Concentrations in *General* Snus Brands and Estimated Daily Intakes from Consumption of *General* Snus Brands

Analyte	Units	Mint PSWL	Nordic Mint PSWL	Classic Blend PSWL	PSOL	PSWL	Winter-green PSWL	Dry Mint PSOM	Loose Snus
		4352	**4876**	**4877**	**4880**	**4881**	**4882**	**4800**	**4852**
Acrylamide	ng/g dw	440	880	850	520	600	620	660	730
Acrylamide	µg/day	2.50	4.95	4.69	3.05	3.48	3.49	5.86	9.81
Aflatoxins B_1		0.0004[¥]	0.0004[¥]	0.0004[¥]	0.0004[¥]	0.0004[¥]	0.0004[¥]	0.0006[¥]	0.0010[¥]
Total Aflatoxins (B_1+ B_2 + G_1 + 21)		0.0080[¥]	0.0080[¥]	0.0078[¥]	0.0083[¥]	0.0082[¥]	0.0080[¥]	0.0126[¥]	0.0190[¥]
Ethyl carbamate		0.120[¥]	0.119[¥]	0.117[¥]	0.124[¥]	0.123[¥]	0.119[¥]	0.188[¥]	0.285[¥]

PS: pouched snus; WL: white large; OL: original large; OM: original mini; dw: dry weight.
[¥] Intake estimates from concentrations <LOD

Intake Estimates from Snus Consumption

Table 8a summarizes the estimated intakes of acrylamide, aflatoxin B_1, total aflatoxins, and ethyl carbamate (concentrations below LOD or LOQ were calculated as described under Section 3.1) assuming 100% extraction. No other extraction information was available.

The estimated acrylamide intake from consumption of 12 g snus is in the range of 2.5 and 5.9 µg/day (1.95-4.95 µg/day, if assuming 12 portions/day for *General Dry Mint PSOM*) for all pouched brands.

Consumption of 32 g of *General Loose Snus* results in an estimated acrylamide intake of 9.8 µg/day.

The estimated aflatoxin B_1, total aflatoxins, and ethyl carbamate intakes from consumption of 12 g pouched snus brands or 32 g of *General Loose Snus* are in the range of 0.0004 and 0.0010 µg/day, 0.0078 and 0.0190 µg/day, and 0.117 and 0.285 µg/day respectively.

Other Trace Level Components – Worst Case

Maximum concentrations of acrylamide (910 ng/g dry weight), total aflatoxins (<1.7 ng/g), and ethyl carbamate (171 ng/g) in Swedish Match snus brands were available from the 2011 Brand Testing data; all concentrations per dry weight.

Using a 95th percentile consumption of 24 g/day snus adjusted for the moisture of each individual product yields estimated maximum intake values up to 10.7, 0.0141, and 1.99 μg/day for acrylamide, total aflatoxins, and ethyl carbamate, respectively, for all pouched snus products except *General Dry Mint PSOM.*

Using a 95th percentile consumption of 24 g/day adjusted for the moisture of *General Dry Mint PSOM* yields estimated maximum intake values of 16.2, 0.0213, and 3.04 μg/day for acrylamide, total aflatoxins, and ethyl carbamate, respectively. When consumption of 24 portions/day is assumed, the estimated maximum intakes are 5.4, 0.0071, and 1.01 μg/day, respectively.

For *General Loose Snus*, using 95th percentile consumption of 77 g/day loose snus and adjusted for the moisture content, yields estimated maximum intake values of 29.4, 0.0389, and 5.53 μg/day for acrylamide, total aflatoxins, and ethyl carbamate, respectively.

Comparison with Intake from Dietary Sources

The estimated daily intake of acrylamide from average snus consumption is below the range of averages of dietary intakes in several countries including the US, even under worst case conditions of pouched snus consumption (ATSDR 2009; see Table 8b). Under worst case conditions of *General Loose Snus* consumption, the estimated daily intake of acrylamide from snus consumption is within the range of averages of estimated dietary intakes and less than four times lower than the current RfD (EPA 2010; see Table 8b).

The estimated daily intake of total aflatoxins from snus consumption is, even under worst case conditions (based on concentrations below LOD), below the average or range of dietary intakes for the US or EU, respectively (JECFA 2007; see Table 8b).

The estimated daily intake of ethyl carbamate from average snus consumption is below the range of dietary intakes in several countries including the US and even under worst case conditions of pouched snus consumption it is within this range (EFSA 2007; JECFA 2005; see Table 8b). Under worst case conditions of *General Loose Snus* consumption, the estimated daily intake of ethyl carbamate is slightly above of the range of estimated dietary intakes, but within the range of intakes estimated by EFSA (EFSA 2007) for the 95th percentile consumption level of different types of alcoholic beverages.

Table 8b: Other Components: Concentrations in Foods and Estimated Dietary Intakes

Other	IARC Group	Concentrations in Food	Estimated Daily Intake from Food and/or Beverages	Guideline Values and Health Basis#
Acrylamide	2A	5–50 µg/kg in heated protein-rich foods, higher concentration of 150 to 4,000 µg/kg in carbohydrate-rich foods, such as potato, beetroot, potato products, and crisp bread (ATSDR 2009).	US and other EU countries, average estimated long-term intake data: 21-56 µg/d. (ATSDR 2009)	RfD: 0.002 mg/kg/d, based on degenerative nerve changes in 2-year drinking water studies (EPA 2010) MRL(intermediate): 0.002 mg/kg/d based on animal studies on neurological effects in males (most sensitive) and females (ATSDR 2009).
Aflatoxins	1 (natural occurring, B_1, G_1, M_1)	< 0.1 to 80 of µg/kg in maize and peanuts, depending on source, food type, climate, storage conditions (IARC 2012a).	Total aflatoxins US, mean: 0.162 µg/d* EU, range of means: 0.056-0.14 µg/d* (JECFA 2007)	Maximum limit: 20 µg/kg brazil nuts, pistachios, almonds, hazelnuts and figs, based on possible effects on the rates of liver cancer (JECFA 2007).
Ethyl Carbamate (urethane)	2A	Fermented foods: 0.2-16 µg/kg in bread, kimchi, yogurt, cheese and soy sauce (JECFA 2005) Alcoholic beverages: 5 µg/L wine and beer, 21 µg/L spirits other than fruit brandy, 260 µg/L fruit brandy (EFSA 2007).	US, Denmark, South Korea, Switzerland, range of means: 1-4 µg/d (JECFA 2005). Whole population (15 years+): 2-3 µg/d; Alcohol consumers only: 2-4 µg/d; 95th percentile of consumption level different types of alcoholic beverages: 1-34 µg/d (EFSA 2007).	BMDL: 0.3 mg/kg/d for incidence of alveolar and bronchiolar neoplasms in male and female mice, based on food intakes (15 ng/kg/d), the resulting MOE is 20 000. With the inclusion of alcoholic beverages in the estimated intakes (80 ng/kg/d) the resulting MOE is 3800 (JECFA 2005).

BMDL: benchmark dose levels; MOE: margin of exposure; MRL: minimum risk levels; RfD: reference dose
* Based on a body weight of 60 kg, the standard value used for adults in the EU

4.4.7 Summary of Results

The estimated daily intakes of all analyzed PAHs, acetaldehyde, formaldehyde, arsenic, chromium, nickel, mercury, selenium, acrylamide, and aflatoxins, even under worst case conditions and assuming 100% extraction, are within or below the average or range of estimated dietary intakes of these components. NDMA intake even under worst case conditions of snus consumption is below the range of the estimated combined intake of NDMA from air, water and food, however, because of the limited amount of data for dietary exposure, confidence in this comparison for NDMA is low.

The estimated daily intakes of beryllium under average snus consumption, cadmium under worst case conditions of *General Loose Snus* consumption, and lead under worst case conditions of snus consumption, adjusted to an extraction rate of 10-50%, are all below or similar to the average dietary intakes of these metals.

The estimated daily intake of Po-210 and uranium (radioisotopes), assuming 100% extraction and average pouched snus consumption, and for ethyl carbamate under worst case conditions of pouched snus consumption, are close to the range or average or are within the range of average dietary intakes.

Under worst case conditions of snus consumption, Po-210 is on the upper end of what has been reported for dietary intakes in various countries; in particular, seafood and fish products are a background source of this radioisotope. Under worst case conditions of *General Loose Snus* consumption, ethyl carbamate is within the range (on the lower end) of intake estimated for the 95th percentile consumption level of different types of alcoholic beverages.

Under worst case conditions assuming a conservative 100% extraction rate, the estimated uranium (radioisotopes) intake from pouched snus products and *General Loose Snus* is higher than the estimated usual dietary intake. This estimated intake from snus is, however, lower than TDIs and RfDs established based on kidney toxicity. It should also be noted that, although no values for extraction of uranium from snus were available, it is likely much lower than 100%.

While the estimated daily intake of crotonaldehyde from average snus consumption is above the estimated usual dietary intake, it is within the range of amounts that may be ingested from consumption of 100 to 200 g of certain meats or fish and less than what might result from drinking alcoholic beverages, such as a glass of wine.

Dietary intake estimates were not available for acrolein, NSAR, NDELA, and most individual VNAs. Intake of total VNAs (10 VNAs) from average snus consumption was similar to what has been reported for dietary intake by one author for the sum of only four VNAs.

The estimated daily intake of acrolein from average snus consumption is approximately 10 times lower than the current RfD for acrolein. Even under worst case conditions of snus consumption, the intake of NSAR is within the range of amounts that may be ingested from a small portion of smoked meat. Similarly, NDELA intake from snus consumption is likely in the range of what might be ingested from a small portion of cured meat, but due to the variability of the analytical data for NDELA in the snus products and the lack of reliable data for concentrations in foods, little confidence is given to the comparison of this component.

5 Discussion and Conclusions

This report presents a comparison of estimated daily intakes of FDA-listed HPHCs (and additional components measured by Swedish Match) from consumption of Swedish Match snus products with intakes from the diet. The exceptions are the tobacco-specific nitrosamines (TSNAs), for which a comparison with estimated exposure from smoking was made, and the alkaloids, for which intakes from snus are summarized, but not further compared to intakes from other sources. For a comparison of nicotine intake from snus consumption versus smoking the reader is referred to the ENVIRON Snus Monograph (2013).

To estimate HPHC intakes from snus consumption, the average concentrations in each of the eight Swedish Match snus products investigated were obtained from a recent company report that compiled and discussed these data. Similarly, to estimate “worst case” exposures from snus consumption, maximum values were obtained from Swedish Match Brands Testing data of several snus products, not specific to the eight products. Average and upper bound snus consumption was obtained from a recent survey of snus users in Sweden. Where supported by research, adjustments for extraction of HPHCs from snus were made.

For the comparison to dietary intakes, average population-based intakes were obtained from public health agencies, and comparisons to health-based guidelines were also drawn where these values were available for the specific HPHCs. In instances where neither of these values were available, intakes estimated from consumption of certain foods provides context.

For the comparison to smoking, an average of 20 cigarettes per day was assumed, and adjustments for absorption were made. For TSNAs and for some of the other potential carcinogens detected in Swedish snus, cancer risk estimates from published risk assessments were presented and discussed.

Generally, for the 39 HPHCs and additionally analyzed VNAs and PAHs discussed in this report, concentrations were in a close range for all snus products on a per gram basis. Variability in the estimated intakes was largely the result of different portion sizes, consumption patterns, and, to some extent, differences in moisture contents of the products.

Comparisons of the estimates of average and upper bound HPHC intakes from use of any of the eight Swedish Match snus products compared to usual or customary intakes of these components from consumption of foods shows that use of snus results in intakes that are generally either lower or similar to those from food. Much like exposure from foods, however, exposure to these components from snus use is variable and dependent on an individual’s product use pattern. This analysis, a comparison between intakes of HPHCs, is not intended to address health risks. Any impact on health risks from the intake comparisons can be inferred from those components in common to both Swedish snus and foods; that is, that any health risks from these exposures would be those that might be subsumed under a usual human diet. It should be noted though that any comparison of intakes from snus versus diet does not account for potential local effects on the oral mucosa, which are best determined in clinical and/or epidemiological studies.

Comparison of the exposure estimates for HPHC components that are part of snus but not part of the diet, such as nicotine and TSNAs, shows that intakes from average snus use are similar to exposure from average cigarette smoking. These conclusions are based on several assumptions about extraction and absorption, which may have some uncertainties. It is also not known how the differences in routes of exposure between exposure to cigarettes via inhalation and Swedish snus via the oral route might contribute to health risks even if ultimate exposures to users are about the same.

The strengths of this analysis include the conservative assumptions used in calculating the estimated exposures from Swedish snus as well as for the comparator exposures. The component concentrations that were below the laboratory limits of detection (LOD) were assumed to have a distribution below the LOD and used to generate estimated exposures for several of the HPHCs. The upper range of extractions was also used so as not to underestimate the amount of an HPHC that might be extracted in the mouth during snus use. As discussed in the report, the comparisons with intakes from food assume similar extraction and uptake of the HPHCs from food and snus, which is likely not the case, as absorption (and thus exposure) from foods is likely to be more complete because of swallowing and digestion in the gastrointestinal tract.

Sources of variability that contribute to uncertainty in the estimates include use of a single (recent) year of annual mean HPHC concentrations in the eight Swedish Match snus products. Variability within the year, and concentrations from previous years were not considered. The worst case calculations, however, which used the highest reported HPHC concentration from additional Swedish Match data, and the reported upper bound daily snus consumption, would be expected to capture some of the variability in the laboratory measurements such that estimated exposures from use of Swedish snus for most contemporary users would not likely be higher than calculated in this report. Actual internal/systemic exposures can be measured by use of appropriate exposure biomarkers.

Because the amounts of HPHCs in foods are also highly variable, estimates of human exposures, which reflect not only the amounts in foods, but factors such as use patterns, extraction and absorption, are also variable. The dietary estimates are not intended to apply to any one individual but are population averages where these data were available and are meant to represent usual intakes.

Though the exposure estimates and cancer risks presented in this report support the epidemiological research on Swedish snus, in which no increased cancer risk has been observed for cancers at sites observed in animals exposed to TSNAs, such as oral and lung cancers, there are some inconsistencies in the epidemiology for other cancer sites, such as pancreatic cancer, which remain to be confirmed by further research.

Clearly, however, the HPHC exposures to users of Swedish snus are generally no more than that from foods, and for HPHC components unique to tobacco, namely nicotine and TSNAs, exposures from Swedish snus are no more than that from smoking.

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Appendix A

Begemann P, Mudasiru O, Ward C, Curvall M, and Rutqvist LE. 2014. Estimated HPHC Intakes from Snus Consumption: Comparison with Dietary Intakes Presented at the 52nd Society of Toxicology Annual Meeting, Phoenix, Arizona. March 27, 2014

Es ima ed HPHC Intakes from Snus Consump ion Compa ison wi h Die ary Intakes

P ra eg ma n Om boa Mu a i u Ca o W rd EN I ON; M rg r ta u val a s E k Ru q st wed h Ma ch

A S RA T

M h 8 00 fi h b d fid b d
b k I 0 2 h S DA I d I fi I 1 0 h fi l
I fi l H H I b d d
k h d h h I d d h
h b h d d I k fi
I H HC fi fi d S d h fi fi
k fi h d

A d b d I fi S P C
d d I H d I I S hM h S I
d d
h I I d h h h H HC
fi M b d d b d d I
F h d k I
b d k fi I h h d I
fi d d H HC b I h I b I
fid O] k O / 2
h P
I I h fi fi d F I k fi I I d
AH d d I I d d fi
d d d 00 b I h
h h fi d k U I
h d d h I I d
k b fi k fi d b I fi
d k
h b k fi P C d d d I
dd h h k fi h I d I I fi
d L fi h h d
d k fi P C fi d fi d h
d h fi k I h h d
fi fi d b h h
h I I d h I

O J CT VE

h b h d h d d I k fi
P C fi h k fi h d h d
d h b fi P C fi fi h
d S d h fi d
O I h U F A fi d H C I k I b h
I I h b I d I I d d
fi I

M THO S

h U DA HC I b d / k
h h fi fi h fi I fi h Ih
d I d fifi d I I
d fifi d dd

E i H C I k f S C i

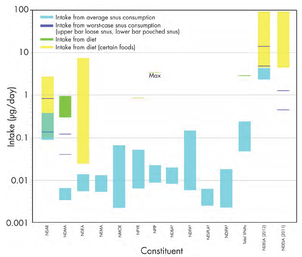
D f h d I S d h d f M h d
I d b I d ll
d)
A H HC h h d I d
12 b M d fi / k
A b l HC f SM b d 0 1
d fi
C d b I h I d f
D O d OD OQ √ U E A 0 0
H d R 1 9)
5 d I
fi k h h h fi D d I 0 9)
P d ( ) 2 d 24 d
N b d d 12 d 4 /d 0 3 /)
L ( ) 2 77 d (65 /)
A 10 f I d
h I I h d d d

$$Intake\ (\mu g/day) = concentration\ \left(\frac{\mu g}{g}\ dry\ weight\right) \times \frac{100 - moisture(\%)}{100} \times consumption\ \left(\frac{g}{day}\right)$$

E i H C I k f Di

S I d h f
I b d d k h bl
fi d d b d
h P C
H hb d I f I d I h h h
D M U A S R fi d I
h d I b d fi I d

Fi 1 N Ni C d Oh h T NA I k f S C i I f i


Intake from average snus consumption
Intake from worstcase snus consumption (upper bar loose snus, lower bar pouched snus)
Intake from diet
Intake from diet (certain foods)
Intake (µg/day)
100
10
1
0.1
0.01
0.001
Max
NDA
NDA
NDA

ERRATUM

"Estimated HPHC Intakes from Snus Consumption: Comparison with Dietary Intakes" by Begemann P, Mudasiru O, Ward C, Curvall M, and Rutqvist LE. 2014. Presented at the 52nd Society of Toxicology Annual Meeting, Phoenix, Arizona. March 27, 2014.

In this poster, in Figure 4 text for lead (Pb), the $BMDL_{10}$ 1.50 µg/kg/d (cardiovascular effects) should read $BMDL_{01}$ 1.50 µg/kg/d (cardiovascular effects)