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Office of Science
Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

**Re: PARTIAL RESPONSE (REQUESTS 31-34) to AUGUST 10, 2018 ADVICE/INFORMATION
REQUEST for PM0000427-PM0000432 and MR0000068-MR0000073**

Dear Drs. Rosenfeldt and Kittner:

RAI Services Company ("RAIS")¹ hereby submits the following, on behalf of R.J. Reynolds Tobacco Company ("RJRT"), in response to the United States Food and Drug Administration's ("FDA") Center for Tobacco Products ("CTP") August 10, 2018, ADVICE/INFORMATION REQUEST letter regarding RAIS's submission of Premarket Tobacco Applications ("PMTAs") and Applications Seeking a Modified Risk Tobacco Product Order ("MRTP Applications"), submitted under Section 910(b) and Section 911(d) of the Food, Drug, and Cosmetic Act ("FDCA"), respectively, on March 30, 2017 for the following tobacco products:

- PM0000427/MR0000072, Camel Snus Robust
- PM0000428/MR0000070, Camel Snus Mellow
- PM0000429/MR0000069, Camel Snus Frost Large
- PM0000430/MR0000071, Camel Snus Mint

¹ RAI Services Company ("RAIS") bears primary responsibility for regulatory compliance for Reynolds American Inc.'s operating companies, including R.J. Reynolds Tobacco Company ("RJRT"), American Snuff Co., LLC ("ASC"), Santa Fe Natural Tobacco Company, Inc. ("SFNTC"), and R.J. Reynolds Vapor Company ("RJRV"). References to RAIS in this letter refer to itself and RJRT where applicable.

- PM0000431/MR0000073, Camel Snus Winterchill
- PM0000432/MR0000068, Camel Snus Frost

This response refers to Requests 31-34 in the aforementioned ADVICE/INFORMATION REQUEST. These questions are not deficiencies, but instead are requests for additional information pertaining to the Environmental Assessments submitted in the Camel Snus MRTPAs/PMTAs (Section 5_ENVIMP). In this response, we have repeated CTP's requests, verbatim and in bold italics, followed by RAIS's response.

Please note that the enclosed response may contain confidential commercial and non-public trade secret information belonging to RAIS, RJRT, or RJRT's vendors. All such confidential and trade secret information is exempt from public disclosure under § 301(j) and § 906(c) of the FDCA, 5 U.S.C. § 552(b)(4), 18 U.S.C. § 1905, and 21 C.F.R. § 20.61 and any similar or related laws and regulations. RAIS and RJRT respectfully request that FDA maintain the confidentiality of this information.

Should you have any questions or require any additional information, please contact me at your earliest convenience.

Respectfully submitted,

P.P.



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FDA-Listed Requests for Information and RAIS Response

31. Your MRTPAs/PMTAs lack information regarding the marketing status of the new products. This information is used to assess the environmental impact of manufacturing, use, and disposal of the new products. Provide the following information in the included table. Provide this information in pounds and metric tons.

- a. If the products are currently marketed, provide the current market volume information.*
- b. Provide the first- and fifth-year market projections for the products.*

STN	Unit	Current Year Market Volume	First-Year Projected Market Volume	Fifth-Year Projected Market Volume
MR0000068/PM0000432	Pounds			
	Metric Tons			
MR0000069/PM0000429	Pounds			
	Metric Tons			
MR0000070/PM0000428	Pounds			
	Metric Tons			
MR0000071/PM0000430	Pounds			
	Metric Tons			
MR0000072/PM0000427	Pounds			
	Metric Tons			
MR0000073/PM0000431	Pounds			
	Metric Tons			

RAIS RESPONSE TO REQUEST 31

For Request 31, FDA requests current market volume information for the Camel Snus products that are currently marketed, and first- and fifth-year market projections to assess potential environmental impact. RAIS submitted 18 Environmental Assessments (“EAs”) for the Camel Snus MRTPAs/PMTAs (see Section 5_ ENVIMP) that project increases in Camel Snus volume by style, and associated decreases in cigarette volume over a five-year period (i.e., 2018-2022). In order to address FDA’s request, RAIS provides current, first- and fifth-year market projections in the tables below (Tables 1-3).

To recap, three EAs per style were provided to account for each of the three Advertising Executions submitted in the MRTPAs (see Section 5_ ENVIMP for all 18 EAs and Section 4_LABEL, specifically “Advertising Execution 1.pdf”, “Advertising Execution 2.pdf”, and “Advertising Execution 3.pdf” for the 3 Advertising Executions). Projected volumes associated with each Advertising Execution scenario reflect the number of cigarette smokers who will switch from cigarette smoking to exclusive Camel Snus use following exposure to the proposed modified-risk advertising execution. RAIS evaluated a five-year period of 2018-2022, consistent with the stated duration of a MRTP order when all post-market surveillance requirements are fulfilled.

For example (and to illustrate this point across all styles), in Section 5.1 “Camel Snus Frost: Advertising Execution #1,” the increased volume of Camel Snus Frost was projected using the

results from the likelihood of use studies with Advertising Execution 1 modified-risk materials and the current market share of Camel Snus Frost in 2015 (See Section titled, “Environmental Introduction Due to Proposed Action”, specifically Table titled, “Likelihood of Use Study Results”, in each of the 18 EAs in Section 5 of the Camel Snus MRTPAs/PMTAs). It was estimated that a MRTP order with Advertising Execution 1 exposure could result in ~52,000 smokers switching from smoking to exclusive use of Camel Snus Frost during 2018 – 2022, resulting in a decrease of ~300 million cigarettes smoked per year, assuming an average use rate of ~16² cigarettes per day. An additional 124,767 pounds of Camel Snus Frost will be manufactured based upon those switchers using 5 pouches of Camel Snus Frost (0.6 g) per day.

As found in Section 5 of the MRTPAs/PMTAs, all six Camel Snus styles that are the subject of the MRTPAs/PMTAs are currently commercially available in the United States. For the purposes of FDA’s current request, RAIS utilizes calendar years 2018 for current Camel Snus market volume and projected first-year (2019) and fifth-year (2023) volumes using the logic and assumptions discussed above and detailed within the EAs provided in the MRTPAs/PMTAs. Current, first- and fifth-year projections for all Camel Snus styles are provided in [Tables 1-3](#).

As explained in detail in the EAs submitted in the MRTPAs/PMTAs, any potential environmental impact from increased Camel Snus volumes is offset by the subsequent decreases in the volume of cigarettes manufactured and used. Thus, MRTP orders for the six Camel Snus styles would result in little, if any, effect on manufacturing emissions and introduction of waste materials into the municipal waste stream other than the fact that a much greater proportion of waste material is recyclable. MRTP orders for the six Camel Snus styles are anticipated to significantly reduce energy and natural resource consumption, as well as, reduce greenhouse gas emissions. In addition, these orders will alter the biopersistence/biodegradability profile of tobacco products in a positive manner by reducing cigarette butt waste and environmental tobacco smoke emissions (see Section 5 of the MRTPAs/PMTAs).

In summary, per 21 CFR 25.40³, RAIS has generated and previously submitted 18 EAs that take into consideration the potential environmental impact(s) of MRTP authorization orders for proposed modified-risk advertising. All six Camel Snus styles are currently commercially available in the U.S. and authorization of Premarket Tobacco Product Applications (PMTAs) for the six Camel Snus styles would not change the existing environmental condition.

² Cigarettes smoked per day on average is a calculated value based on data from the Treasury Alcohol and Tobacco Tax and Trade Bureau (TTB) Statistical Reports from 2011 - 2015 and the number of adult smokers in 2015, which is estimated from the adult population regression and the incidence regression. See Section 5 of the Camel Snus MRTPAs/PMTAs.

³ FDA. Code of Federal Regulations Title 21, Volume 1. Revised April 1, 2018. Section 25.40 (21CFR25.40). <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=25.40>

Table 1: Current and Projected Market Volumes for Camel Snus Products – ADVERTISING EXECUTION#1 (CONTAINS CONFIDENTIAL INFORMATION)				
STN	Unit	Current Year Market Volume*	First-Year Projected Market Volume*	Fifth-Year Projected Market Volume*
MR0000068/PM0000432	Pounds	(b) (4)		
Camel Snus Frost	Metric Tons			
MR0000069/PM0000429	Pounds			
Camel Snus Frost Large	Metric Tons			
MR0000070/PM0000428	Pounds			
Camel Snus Mellow	Metric Tons			
MR0000071/PM0000430	Pounds			
Camel Snus Mint	Metric Tons			
MR0000072/PM0000427	Pounds			
Camel Snus Robust	Metric Tons			
MR0000073/PM0000431	Pounds			
Camel Snus Winterchill	Metric Tons			
FDA-provided information repeated verbatim and in bold italics in the table. *Current and projected market volumes (pounds and metric tons) represent the volume of pouches, which includes the weights of the tobacco and fleece material.				

Table 2: Current and Projected Market Volumes for Camel Snus Products – ADVERTISING EXECUTION#2 (CONTAINS CONFIDENTIAL INFORMATION)							
STN	Unit	Current Year Market Volume*	First-Year Projected Market Volume*	Fifth-Year Projected Market Volume*			
MR0000068/PM0000432	Pounds	(b) (4)					
Camel Snus Frost	Metric Tons						
MR0000069/PM0000429	Pounds						
Camel Snus Frost Large	Metric Tons						
MR0000070/PM0000428	Pounds						
Camel Snus Mellow	Metric Tons						
MR0000071/PM0000430	Pounds						
Camel Snus Mint	Metric Tons						
MR0000072/PM0000427	Pounds						
Camel Snus Robust	Metric Tons						
MR0000073/PM0000431	Pounds						
Camel Snus Winterchill	Metric Tons						
FDA-provided information repeated verbatim as							
*Current and projected market volumes (pounds and metric tons) represent the volume of pouches, which includes the weights of the tobacco and fleece material.							

**Table 3: Current and Projected Market Volumes for Camel Snus Products – ADVERTISING EXECUTION#3
(CONTAINS CONFIDENTIAL INFORMATION)**

<i>STN</i>	<i>Unit</i>	<i>Current Year Market Volume*</i>	<i>First-Year Projected Market Volume*</i>	<i>Fifth-Year Projected Market Volume*</i>
<i>MR0000068/PM0000432</i>	<i>Pounds</i>	(b) (4)		
Camel Snus Frost	<i>Metric Tons</i>			
<i>MR0000069/PM0000429</i>	<i>Pounds</i>			
Camel Snus Frost Large	<i>Metric Tons</i>			
<i>MR0000070/PM0000428</i>	<i>Pounds</i>			
Camel Snus Mellow	<i>Metric Tons</i>			
<i>MR0000071/PM0000430</i>	<i>Pounds</i>			
Camel Snus Mint	<i>Metric Tons</i>			
<i>MR0000072/PM0000427</i>	<i>Pounds</i>			
Camel Snus Robust	<i>Metric Tons</i>			
<i>MR0000073/PM0000431</i>	<i>Pounds</i>			
Camel Snus Winterchill	<i>Metric Tons</i>			

FDA-provided information repeated verbatim and in bold italics in the table.

*Current and projected market volumes (pounds and metric tons) represent the volume of pouches, which includes the weights of the tobacco and fleece material.

32. Your MRTPAs/PMTAs lack detailed information about how the new products will be packaged. Packaging materials include shipping cases. This information allows for an accurate assessment of the solid waste generated from disposal of the products. Provide answers to the following questions to address packaging details in the included table.

- a. What is the composition of the shrink tape that is used to seal each container? What is the composition of the overwrap film encasing each sleeve? What is the weight and composition of the retail box (if any) containing the “sleeves” and the number of “sleeves” per retail box? What is the weight and composition of the shipping case and the number of “sleeves” or retail boxes (if any) per shipping case?**

Packaging Component	Composition	Weight (grams)	Number
(b) (4)			

RAIS RESPONSE TO REQUEST 32

For Request 32, FDA requests additional information on the material types and weights for packaging components of all six Camel Snus styles that are the subject of the MRTPAs/PMTAs. In the table provided by FDA, some Camel Snus packaging information was included. In [Table 4](#), RAIS has repeated verbatim and in bold italics the FDA-provided information and has filled in the remainder of the table with the requested information.

RAIS noticed upon responding to FDA’s request, that our EAs submitted in Section 5 of the Camel Snus MRTPAs/PMTAs incorrectly listed ‘Shrink tape’ as one of the packaging components for the Camel Snus styles. However, the six Camel Snus styles subject of the MRTPAs/PMTAs do not utilize shrink tape as a packaging component, but instead incorporate a shrink band (see Table 3.2-30: Packaging Materials for Camel Snus Products and Figure 3.2-1: Illustration of Camel Snus packaging provided in Section 3 of the Camel Snus MRTPAs/PMTAs). [Table 4](#) has been updated to reflect the correct terminology of this packaging component. Additionally, and as noted in [Table 4](#), Camel Snus tins are not packaged in retail boxes, but are instead combined in sleeves. One sleeve consists of 5 Camel Snus tins wrapped in overwrap film (see Section titled “Identification of the Product that is Subject of the Proposed Action” in the Environmental Assessments provided in the Camel Snus MRTPAs/PMTAs). Each shipping case contains 18 sleeves.

Additional packaging material information for the Camel Snus styles subject of the MRTPAs/PMTAs was provided in RAIS’s October 31, 2018 Amendment (RAIS RESPONSE TO DEFICIENCY 5e).

Table 4. Camel Snus Packaging Information			
<i>Packaging Component</i>	<i>Composition</i>	<i>Weight (grams)</i>	<i>Number</i>
(b) (4)			
<p>FDA-provided information repeated verbatim and in bold italics in the table.</p> <p>*The FDA-provided table in Request 32 and the packaging information provided in the EAs submitted in Section 5 of the Camel Snus MRTPAs/PMTAs incorrectly listed (b) (4) as a packaging component. RAIS has updated this to (b) (4) in this table to correctly identify the packaging component utilized in the Camel Snus products.</p> <p>(b) (4)</p> <p>“N/E” indicates not employed. “N/A” indicates not available.</p>			

RAIS notes that custody of the shipping cases ends at retail and not with the consumer. Furthermore, the shipping cases used for transport of Camel Snus are compositionally identical to those used for other RAI tobacco products and comprise materials that can be, and are likely, recycled by the retailers.

33. Your MRTPAs/PMTAs state that the product packaging “lid interior incorporates an internal seal technology” to “maintain the freshness and quality of the product”, and the seal material is composed of Plastisol. However, you did not discuss the environmental impact(s) of the disposal of the Plastisol. This information allows for an accurate assessment of the solid waste generated from disposal of the products. Provide a description of the environmental impact(s) of the seal material, Plastisol, from disposal of the products.

RAIS RESPONSE TO REQUEST 33

The six Camel Snus styles that are the subject of the MRTPAs/PMTAs are packaged in a two-pieced metal container fabricated out of tin-plated steel that is commonly utilized in various food containers. The lid interior of the metal containers incorporate an internal seal composed of food grade plastisol^{4,5} that functions to provide a seal between the lid and the base to support closure. As a result of the application process, in which the heated plastisol is applied directly to the lid and cooled while in contact with the base, the plastisol creates a vacuum seal for the metal container. The product packaging (including the plastisol) can enter the general U.S. consumer recycling stream. As stated in the Environmental Assessment (see Section 5, sub-section titled “Environmental Introduction as a Result of Disposal after Product Use”), the product’s packaging tins include instructions to avoid littering (“Do Not Litter”) and to recycle the tins after use (“This Container is Recyclable”). It is anticipated that the tins will be recycled following use of the product and that the product packaging, including the plastisol, will be processed through the recycling stream. Therefore, it is expected that the environmental impact would be minimal from disposal of the tin lid and plastisol internal seal.

⁴ FDA. Guide to Inspections of Low Acid Canned Food Manufacturers: Part 3.

<https://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm109763.htm>

⁵ FDA. Code of Federal Regulations Title 21, Volume 3. Revised April 1, 2018. Section 177.1210 (21CFR177.1210).

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=177.1210>

34. Your MRTPAs/PMTAs state that “the tobacco and fleece components of the used pouch are biodegradable”, but you did not provide the ingredients and biodegradation byproducts. This information is used to accurately assess the environmental impact(s) of disposal of the products. Provide details on the ingredients and biodegradation byproducts of the tobacco and fleece components of the snus pouches and include a description of their environmental impact(s) from disposal.

RAIS RESPONSE TO REQUEST 34

As described in Section 5 of the Camel Snus MRTPAs/PMTAs, consumers dispose of used Camel Snus pouches through deposit into municipal solid waste (MSW) landfills or as litter. The geographical distribution of waste from disposal after product use should correspond to current patterns of product use throughout the United States.

In the event the product is not disposed of into the MSW landfills, but instead as litter, the fleece pouch and tobacco would be improperly disposed of into the environment. Taking that into consideration, RAIS understands FDA’s Question 34 to be a request for ingredients and by-products of the tobacco and fleece components of the Camel Snus styles subject of the MRTPAs/PMTAs in order to understand the potential environmental impact if the product was improperly disposed of as litter into the environment following use.

RAIS notes that in Deficiency 5d, FDA had a related request, “[Y]our MRTPAs lack information about the individual ingredients comprising the fleece pouch material.” In RAIS’s October 31, 2018 Amendment, RAIS responded to Deficiency 5d by providing the full ingredient disclosures from each of the fleece suppliers. (b) (4)

(b) (4)

For ease of FDA review, RAIS provides that information again herein as well as a description of the environmental impact from the fleece pouch materials and tobacco if disposed of as litter into the environment following use.

Fleece Components

RJRT employs a portioning material, referred to as fleece, to produce the portioned unit of Camel Snus. (b) (4)

(b) (4). Table 5 and Table 6 list the fleece ingredients from each fleece supplier, respectively. These formulations are the trade-secret property of RJRT’s suppliers.

(b) (4)



(b) (4)



⁶ FDA. Code of Federal Regulations Title 21, Volume 3. Revised April 1, 2018. Section 177.2260 (21CFR177.2260). <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=177.2260>

⁷ FDA. Code of Federal Regulations Title 21, Volume 3. Revised April 1, 2018. Section 176.170 (21CFR176.170). <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/cfrsearch.cfm?fr=176.170>

⁸ FDA. Code of Federal Regulations Title 21, Volume 3. Revised April 1, 2018. Section 176.180 (21CFR176.180). <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=176.180>

⁹ The German Federal Institute for Risk Assessment (BfR).

(b) (4)

Tobacco

As discussed above, the ingredients from the fleece material are not anticipated to substantially impact the environment in the event they were discarded improperly as litter following use. In the event that a snus pouch is improperly disposed of, the tobacco within the pouch will also be disposed of into the environment. Tobacco is naturally occurring and is not anticipated to have an impact on the environment. Further, all six styles of Camel Snus are manufactured with an identical, common blend of low-toxicant tobaccos.

Within the context of the Camel Snus styles, nicotine represents the most concentrated constituent that is expected to be of ecotoxicological relevance.¹⁴ Unlike combusted cigarettes, snus remains principally intact following use. Residual nicotine is expected to be present in the

http://www.bfr.bund.de/en/the_german_federal_institute_for_risk_assessment__bfr_-572.html

¹⁰ FDA. Code of Federal Regulations Title 21, Volume 3. Revised April 1, 2018. Section 177.2800 (21CFR177.2800). <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=177.2800>

¹¹ USFDA. Food Contact Substance (FCN) No. 1582. https://www.accessdata.fda.gov/scripts/fdcc/?set=ENV-FCN&id=1582&sort=FCN_Number&order=DESC&startrow=1&type=basic&search=cellulose

¹² FDA. Code of Federal Regulations Title 21, Volume 3. Revised April 1, 2018. Section 175.105 (21CFR175.105). <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/cfrsearch.cfm?fr=175.105>

¹³ FDA. Code of Federal Regulations Title 21, Volume 3. Revised April 1, 2018. Section 177.2600 (21CFR177.2600). <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/cfrsearch.cfm?fr=175.105>

¹⁴ Lange, I. (2010). Distinct composition and pharmacokinetic profiles of smoke and smokeless tobacco products: Development of an analytical method to highlight nicotine consumption as a doping agent. Master of Science Thesis. Norway: University of Tromsø.

used snus pouch following its use and potential improper disposal of as litter.

A review of public literature indicates that leachate from used and unused combusted cigarettes and cigarette butts that are improperly disposed of as litter may be toxic to marine and freshwater species, with aquatic invertebrates being the most sensitive.^{15,16} Because Camel Snus is a smokeless tobacco product and the tobacco is not burned, it is not expected to contain many of the chemicals of concern that are found in combusted cigarette butts (e.g., tar). However, residual nicotine is expected to be present in the used Camel Snus products and may contribute to the ecotoxicity of leachate.

Any ecotoxicity impacts from residual nicotine via leachate from improper disposal to the terrestrial environment would be isolated and localized. The quantity of nicotine in the new product is not expected to cause localized effects if a single Camel Snus pouch was improperly disposed of to the terrestrial environment. Adverse effects to the aquatic environment from improper disposal of the new product are unlikely for the following reasons: (1) nicotine would be in a very localized area, and organisms would likely avoid the nicotine by moving away from the source^{17,18}; (2) some biodegradation of nicotine in soil would occur before nicotine would reach surface water^{19,20,21}; (3) rainfall would release the nicotine from the new product, dilute it, and transfer it into the surface water or groundwater for further dilution; (4) nicotine has a high biodegradability rate in water resulting in decreasing concentrations over time^{21,22}; and (5) the physical-chemical properties of nicotine indicate that it would not accumulate in aquatic organisms.²³ All of these factors indicate that any potential for effects would be localized, limited and would improve over time without the likelihood of additional inputs of nicotine to the same location.

The fleece materials and tobacco contained within the Camel Snus 0.6 and 1.0 g pouches are expected to be properly disposed of in MSW landfills. In the event they are improperly disposed of as litter, and for the reasons outlined above, the fleece materials and tobacco would not be expected to have a substantial environmental impact.

¹⁵ Slaughter, E., Gersberg, R.M., Watanabe, K., Rudolph, J., Stransky, C., Novotny, T.E. (2011). Toxicity of cigarette butts, and their chemical components, to marine and freshwater fish. *Tob Control*, 20(Suppl_1):i25-i.29.

¹⁶ Novotny, T.E. and Slaughter, E. (2014) Tobacco Product Waste: An environmental approach to reduce tobacco consumption. *Curr Environ Health Rep.* 1(3): 208–216.

¹⁷ Seckar, J., Mari, S., Stavanja, P., Harp, Y., Yi, C., Gardner, & Doi. (2008). Environmental Fate and Effects of Nicotine Released During Cigarette Production. *Environmental Toxicology and Chemistry*, 27(7), 1505-1514.

¹⁸ Savine, J., & Tanabe, L. (1989). Sublethal Effects of Phenanthrene, Nicotine and Pinene on *Daphnia pulex*. *Bull. Environ. Contam. Toxicol.*, 42(5), 778-784.

¹⁹ Wang, H. H., Yin, B., Peng, X. X., Wang, J. Y., Xie, Z. H., Gao, J., & Tang, X. K. (2012). Biodegradation of nicotine by newly isolated *Pseudomonas* sp. CS3 and its metabolites. *Journal of Applied Microbiology*, 112(2), 258-268.

²⁰ Bradley, Barber, Kolpin, McMahon, & Chapelle. (2007). Biotransformation of Caffeine, Cotinine and Nicotine in Stream Sediments. *Environmental Toxicology and Chemistry*, 26(6), 1116-1121.

²¹ EpiWeb 4.1 predicates a half-life for nicotine of 37.5 days in water and 75 days in soil under aerobic conditions. For EpiWeb 4.1 source, see USEPA. (2016b). Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United States Environmental Protection Agency, Washington, DC, USA.

²² Sangster, A., & Stuart, K. (1965). Ultraviolet Spectra of Alkaloids. *Chemical Reviews*, 29, 69-130.

²³ Hansch, C., Hoekman, D., Leo, A., Zhang, L., & Li, P. (1995). The expanding role of quantitative structure-activity (QSAR) in toxicology. *Toxicology Letters*, 79, 45-53.