Quantitative Risk Assessment (QRA) indicates reduced risk potential for carcinogenic and non-carcinogenic effects of the aerosol of Next Generation Products compared to reference cigarette

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1. INTRODUCTION/OBJECTIVES

Smoking is a cause of serious diseases including lung cancer, cardiovascular disease and emphysema. There is scientific agreement that the harmful effects of cigarette smoke are produced by the formation of Harmful and Potentially Harmful Constituents (HPHCs) from tobacco combustion. Recent studies have shown that the aerosol from Next Generation Products (NGPs) contains a limited number of chemical constituents and these are present at significantly lower levels than in cigarette smoke (Rudd *et al.,* 2019, O'Connell *et al*., 2019).

In order to understand the potential relative health risks of NGPs compared to combustible cigarettes, the relative risks of aerosols from tobacco-containing and tobacco-free NGPs were compared to the smoke generated from a reference cigarette. Quantitative Risk Assessment (QRA) is a scientific, evidence-based analytical process that combines chemical and biological data to quantify the probability and potential impact of defined risks (Marano *et al*., 2018). This work will present a comparison of reduced exposure and corresponding potential risks for the myblu™ e-cigarette and Pulze™ heated tobacco (HT) in comparison to the reference cigarette (3R4F). QRA was used to estimate the potential carcinogenic and non-carcinogenic relative risk of all three products.

2. MATERIALS AND METHODS

2.1 Aerosol Chemistry data

The US FDA abbreviated Harmful and Potentially Harmful Constituent (HPHC) list was the focus of this assessment (acetaldehyde, acrolein, 1,3-butadiene, benzene, benzo-a-pyrene, CO, formaldehyde, NNN, NNK, 1-aminonaphthalene, 2-aminonaphthalene, 4-aminobiphenyl, acrylonitrile, ammonia, crotonaldehyde, isoprene and toluene). The levels of these HPHCs in the reference cigarette smoke, myblu™ e-cigarette and Pulze™ heated tobacco aerosol, were obtained from previous studies (Rudd *et al*., 2019; O'Connell *et al*., 2019) and were used for the exposure and relative risk calculation.

2.2 Exposure Consideration

3R4F & HT	e-cigarette
$LADI = \frac{AC \times CPD\ (SPD) \times ED \times EF}{DIR \times AT}$	$LADI = \frac{AC \times (PC \times PV) \times ED \times EF}{DIR \times AT}$

LADI *– Lifetime Average Daily Intake,* ***AC****: analyte concentration;* ***CPD (SPD)****: cigarettes/HT sticks per day (20 for both);* ***ED****: exposure duration (64.4 years);* ***EF****: exposure frequency (356 days);* ***DIR****: daily inhalation rate (20 m³/day);* ***AT****: averaging time (25550 days);* ***PC****: puff count (worst-case 400 puffs);* ***PV****: puff volume (0.055 L)*

2.3 Hazard Identification

Cancer Risk:

Incremental Lifetime Cancer Risk,

ILCR = LADI x IUR

Cumulative ILCR = Σi ILCRi

Non-Cancer Risk:

Hazard Quotient, HQ = LADI ÷ RfC or REL

Cumulative HQ = Σi HQi

Note: For specific toxicity endpoints, respiratory, cardiovascular, or reproductive/developmental, add the HQs for each analyte according to table in section 2.4

IUR *- Inhalation Unit Rate*
REL *- Reference Exposure Level*
RfC *– Reference Concentration*
HQ *- Hazard Quotient*

2.4 Toxicity Values Considered for Risk Assessment

Constituent	CANCER		NON-CANCER		Toxicity Endpoint		
	IUR (µg/m³)⁻¹	Source	RfC/REL (µg/m³)	Source	Respiratory	Cardiovascular	Repro/Develop
Acetaldehyde	2.20E-06	IRIS, 1988	9	USEPA, 1991	X	X	X
Acrolein	N/A	N/A	0.02	USEPA, 2003	X	X	X
Acrylonitrile	6.80E-05	IRIS, 2018	2	USEPA, 1991	X	X	-
4-Aminobiphenyl	6.00E-03	CALEPA, 1992	N/A	N/A	-	-	-
1-Aminonaphthalene	5.14E-04	CALEPA, 1992	N/A	N/A	-	-	-
2-Aminonaphthalene	5.14E-04	CALEPA, 1992	N/A	N/A	-	-	-
Ammonia	N/A	N/A	500	USEPA, 2016	X	-	-
Benzene	7.80E-06	IRIS, 2000	30	USEPA, 2003	X	X	X
Benzo[a]pyrene	6.00E-04	IRIS, 2017	N/A	N/A	-	X	X
1,3-butadiene	3.00E-05	IRIS, 2002	2	USEPA, 2003	X	X	X
Carbon Monoxide	N/A	N/A	23000	CALEPA, 2008	-	X	X
Crotonaldehyde	3.27E-05	TECQ, 2015	10	TECQ, 2015	X	X	-
Formaldehyde	1.30E-05	IRIS, 1988	10	ATSDR, 1999	X	X	-
Isoprene	2.20E-08	TECQ, 2015	N/A	N/A	X	-	-
NNK	1.40E-02	CALEPA, 2001	N/A	N/A	-	-	-
NNK	4.00E-04	CALEPA, 1992	N/A	N/A	-	-	-
Toluene	N/A	N/A	5000	USEPA, 2005	X	-	X

3. RESULTS

3.1 Quantitative Risk Assessment of E-Cigarette Aerosol Constituents Compared to Combusted Cigarette

In Rudd *et al*., (2019) for the e-cigarette aerosol, all the analytes were either below the Limit of the Detection or Quantification within the sensitivity of the analytical methodology and therefore those levels were assigned for the QRA modelling purposes.

Constituent, µg/cig or µg/liter	Mean CC (µg/cig)	Mean E-Cig (µg/L)	LADI CC (µg/m3)	LADI E-Cig (µg/m3)	HQ CC	HQ E-Cig	HQ Ratio E-Cig/CC	Percent Reduction
Acetaldehyde	1511.31	6.36	1390.41	6.43632	154.49	0.715147	0.0046	99.54
Acrolein	175.71	1.59	161.653	1.60908	8082.7	80.454	0.01	99
Acrylonitrile	28.26	0.0339	25.9992	0.0343463	13	0.017173	0.0013	99.87
Ammonia	35.75	<LOD	32.89	<LOD	0.0658	<LOD	<LOD	100
Benzene	102.06	0.0255	93.8952	0.0257595	3.1298	0.000859	0.0003	99.97
1,3-Butadiene	104.06	0.057	95.7352	0.0576526	47.868	0.028826	0.0006	99.94
Carbon monoxide	29760	<LOD	27379.2	<LOD	1.1904	<LOD	<LOD	100
Crotonaldehyde	52.68	1.59	48.4656	1.60908	4.8466	0.160908	0.0332	96.68
Formaldehyde	93.99	0.9545	86.4708	0.965954	8.6471	0.096595	0.0112	98.88
Toluene	197.68	0.0255	181.866	0.0257595	0.0364	5.15E-06	0.0001	99.99

Hazard Index (HI):	Combustible Cigarette:	E-Cigarette:	Ratio E-Cig to CC:	Percent Reduction:
	8.32E+03	81.47	0.009797	99.02

Constituent, µg/cig or µg/liter	CC Mean (µg/cig)	E-Cig Mean (µg/L)	LADI CC (µg/m3)	LADI E-Cig (µg/m3)	ILCR CC	ILCR E-Cig	ILCR Ratio E-Cig/CC	Percent Reduction
1,3-Butadiene	104.06	0.057	95.7352	0.05765263	0.00287	0.00000173	0.0006	99.94
2-Aminonaphthalene	0.0183	0.0012	0.0168	0.00122452	8.66E-06	6.29E-07	0.0727	92.73
4-Aminobiphenyl	0.0037	0.0002	0.0034	0.00024288	0.0000205	0.00000146	0.071	92.9
Acetaldehyde	1511.31	6.36	1390.4052	6.43632	0.00306	0.0000142	0.0046	99.54
Acrylonitrile	28.26	0.0339	25.9992	0.03434627	0.00177	0.0000234	0.0013	99.87
Benzene	102.06	0.0255	93.8952	0.02575945	0.000732	2.01E-07	0.0003	99.97
Benzo[a]pyrene	0.0136	0.0012	0.0125	0.0012144	7.49E-06	7.29E-07	0.0973	90.27
Formaldehyde	93.99	0.9545	86.4708	0.965954	0.00112	0.0000126	0.0112	98.88
Isoprene	584.58	0.04	537.8136	0.04048	0.0000118	8.91E-10	0.0001	99.99
NNK	0.2379	0.0024	0.2188	0.00244904	0.00306	0.0000343	0.0112	98.88
NNN	0.364	0.0024	0.3349	0.00244904	0.000134	0.00000098	0.0073	99.27

Lifetime Cancer Risk (ILCR):	Combustible Cigarette:	E-Cigarette:	Ratio E-Cig to CC:	Percent Reduction:
	1.28E-02	6.9E-05	0.005	99.46

3.2 Quantitative Risk Assessment of Heated Tobacco Product Aerosol Constituents Compared to Combusted Cigarette

In O'Connell *et al*., (2019) for heated tobacco aerosol , the majority of the analytes were either below the Limit of the Detection or Quantification within the sensitivity of the analytical methodology and therefore those levels were assigned for the QRA modelling purposes.

Constituent, µg/cig or µg/stick	Mean CC (µg/cig)	Mean HT (µg/stick)	LADI CC (µg/m3)	LADI HT (µg/m3)	HQ CC	HQ HT	HQ Ratio HT/CC	Percent Reduction
Acetaldehyde	1511.31	125.94	1390.4052	115.865	154.49	12.8739	0.0833	91.67
Acrolein	175.71	2.86	161.6532	2.6312	8082.66	131.56	0.0163	98.37
Acrylonitrile	28.26	0.24	25.9992	0.2208	12.9996	0.1104	0.0085	99.15
Ammonia	35.75	7.1	32.89	6.532	0.0658	0.01306	0.1986	80.14
Benzene	102.06	0.18	93.8952	0.1656	3.1298	0.00552	0.0018	99.82
1,3-Butadiene	104.06	0.4	95.7352	0.368	47.8676	0.184	0.0038	99.62
Carbon monoxide	29760	270	27379.2	248.4	1.1904	0.0108	0.0091	99.09
Crotonaldehyde	52.68	2.19	48.4656	2.0148	4.8466	0.20148	0.0416	95.84
Formaldehyde	93.99	2.64	86.4708	2.4288	8.64708	0.24288	0.0281	97.19
Toluene	197.68	0.46	181.8656	0.4232	0.0364	8.46E-05	0.0023	99.77

Hazard Index (HI):	Combustible Cigarette:	Heated Tobacco:	Ratio HT to CC:	Percent Reduction:
	8.32E+03	1.45E+02	1.75E-02	98.25

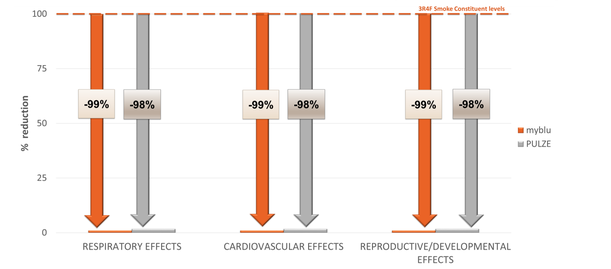
Constituent, µg/cig or µg/stick	Mean CC (µg/cig)	Mean HT (µg/stick)	LADI CC (µg/m3)	LADI HT (µg/m3)	ILCR CC	ILCR HT	ILCR Ratio HT/CC	Percent Reduction
1,3-Butadiene	104.06	0.4	95.7352	0.368	2.87E-03	1.10E-05	0.0038	99.62
2-Aminonaphthalene	0.02	0.0035	0.0168	0.0031832	8.66E-06	1.64E-06	0.189	81.1
4-Aminobiphenyl	0	0.0007	0.0034	0.0006256	2.05E-05	3.75E-06	0.1828	81.72
Acetaldehyde	1511.31	125.94	1390.4052	115.8648	3.06E-03	0.00026	0.0833	91.67
Acrylonitrile	28.26	0.24	25.9992	0.2208	1.77E-03	1.50E-05	0.0085	99.15
Benzene	102.06	0.18	93.8952	0.1656	7.32E-04	1.29E-06	0.0018	99.82
Benzo[a]pyrene	0.0136	0.0017	0.0125	0.0015364	7.49E-06	9.22E-07	0.1232	87.68
Formaldehyde	93.99	2.64	86.4708	2.4288	1.12E-03	3.16E-05	0.0281	97.19
Isoprene	584.58	0.58	537.8136	0.5336	1.18E-05	1.17E-08	0.001	99.9
NNK	0.2379	0.0033	0.2188	0.003036	3.06E-03	4.25E-05	0.0139	98.61
NNN	0.364	0.0033	0.3349	0.003036	1.34E-04	1.21E-06	0.0091	99.09

Lifetime Cancer Risk (ILCR):	Combustible Cigarette:	Heated Tobacco:	Ratio HT to CC:	Percent Reduction:
	1.28E-02	3.64E-04	2.84E-02	97.16

3.3 Estimated Non-cancer Hazard by Endpoint

The modelling performed for the non-cancer hazard estimation on the analytes grouped into endpoint-specific effects. A marked reduction for the respiratory, cardiovascular and reproductive/developmental risks was observed for both Next Generation Products. On average the aerosols from the myblu™ e-cigarette and Pulze™ heated tobacco (HT) had 99% and 98% risk reduction respectively in each endpoint compared to the reference cigarette (3R4F) smoke.

Estimated Non-cancer Hazard for EVP and HT Products Compared to Combusted Cigarette



4. CONCLUSIONS AND OUTLOOK

- The Quantitative Risk Assessment (QRA) methodology serves as a valuable tool for estimating the relative risk associated between products; although it fails to capture whole smoke chemical analyte interactions and synergism and focuses on a limited number of chemical constituents. Based on the results of this QRA tool the aerosols of e-cigarettes and heated tobacco products have the potential for a marked reduction of non-cancer (NCR) and cancer (CR) risks compared to combustible cigarettes. For e-cigarettes the reduced risk is 99.02 and 99.46% for NCR and CR, respectively. For heated tobacco product the reduced risk is 98.25 and 97.16% for NCR and CR, respectively.
- A study from St. Andrews University, UK, recently found that an optimal combination of EVP device settings, liquid formulation and vaping behaviour result in EVP emissions with much less carcinogenic potency than tobacco smoke and estimated EVP emissions having cancer risk <1% compared to tobacco smoke (Stephens, 2018).
- Future work will focus not only on a wider range of aerosol analytes (including the additional HPHC list proposed by the FDA in the PMTA for Electronic Nicotine Delivery Systems guidance document for the industry) but will also assess the impact of transitioning from a combusted cigarette to an e-cigarette exposure on the non-cancer and cancer risk.

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